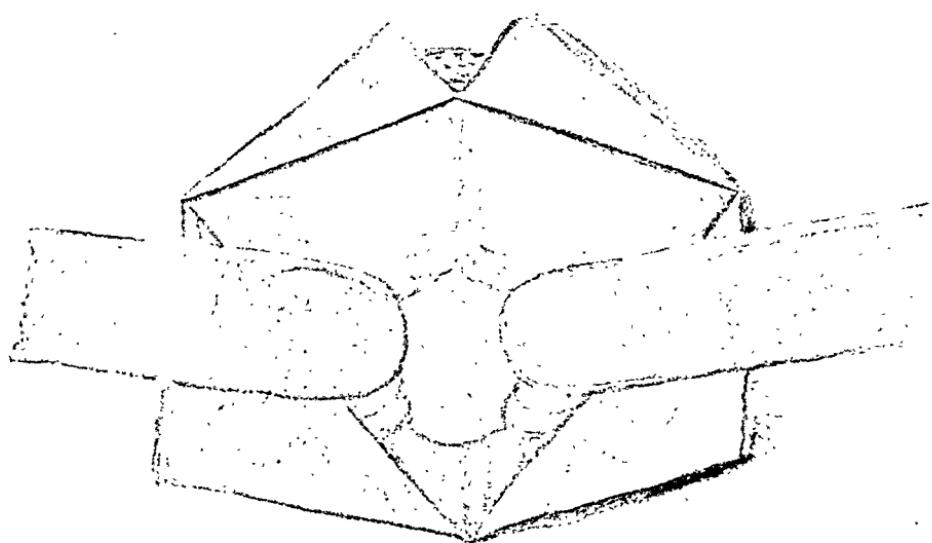


FIG. 1.



ME Willingham

Traumatic cyst of brain, with arachnoid cyst bulging up between cerebellar lobes. (Artist's drawing from operator's sketch.)

Frontispiece, page 101.

INTERNATIONAL CLINICS

A QUARTERLY
OF

ILLUSTRATED CLINICAL LECTURES AND
ESPECIALLY PREPARED ORIGINAL ARTICLES
ON

TREATMENT, MEDICINE, SURGERY, NEUROLOGY, PÆDIATRICS,
OBSTETRICS, GYNÆCOLOGY, ORTHOPÆDICS,
PATHOLOGY, DERMATOLOGY, OPHTHALMOLOGY,
OTOLOGY, RHINOLOGY, LARYNGOLOGY,
HYGIENE, AND OTHER TOPICS OF INTEREST
TO STUDENTS AND PRACTITIONERS

BY LEADING MEMBERS OF THE MEDICAL PROFESSION
THROUGHOUT THE WORLD

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NEW ORLEANS

VOLUME I. FORTY-FIRST SERIES, 1931

PHILADELPHIA AND LONDON

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The clinical clerk, Mr. A. F. Jones, found, on inquiry, that the present illness had begun in March, 1930, some seven months before admission, when the patient slipped and fell on the stairs, and, on attempting to save herself by grasping the railing, wrenched her back. She felt very nervous after the accident and two weeks later began to notice weakness, numbness, and tingling in the right foot, as well as difficulty on walking. She said that "she walked sideways as if drunk" and that she had to stamp her feet upon the floor and to watch where she was walking. The numbness and stiffness soon extended to the foot, the legs and the thighs of both sides, and to the back. A little later on, she noticed "blurring" in the left eye, which, however, cleared up in about two weeks. She consulted a physician who told her that she had "high blood-pressure" and advised her to go to the Johns Hopkins Hospital for study. She entered that hospital on June 19th and remained there two and a half weeks, during which time careful studies were made not only of the nervous symptoms and signs, but of her condition as a whole. Her temperature at that time was slightly elevated, the pulse rate was 120, and the blood-pressure was registered as 160 systolic and 100 diastolic. There was numbness and stiffness of the gait, weakness of the left leg, loss of vibration sense in both legs, exaggeration of the deep reflexes of the lower extremities, and ankle clonus and a positive Babinski sign on the left. Examination of the blood in June revealed a secondary anemia (R. B. C. 4,000,000; hemoglobin 74 per cent), and on dental consultation, extensive oral sepsis was found and all of the patient's teeth were extracted. The urine and the stool were negative and the Wassermann test of the blood serum was also negative. Lumbar puncture revealed no abnormalities of the cerebrospinal fluid. Studies of the blood chemistry showed no increase of the non-protein nitrogen and the sugar content (108 milligrams per cent.) was within normal limits. Examination of the stomach contents showed 32 acidity per cent. (total), and free hydrochloric acid was present. On tests of renal function no impairment was found. Roentgenograms of the heart, lungs, spine and knees were negative. The examination of the eyes revealed "early choking of the left nerve head."

The patient returned to the Johns Hopkins Hospital Dispensary (neurological division) on July 22, 1930, where it was found that the neurological symptoms had advanced; the spastic paresis in the lower extremities had become more pronounced. On the other hand, the optic neuritis had improved; the note was made that the left eye also had cleared up and looked normal.

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Professor Barker's University of Maryland Clinics

SPASTIC PARAPLEGIA AND VISUAL DISTURBANCES
(PROBABLY DUE TO DISSEMINATED SCLEROSIS),
OCCURRING IN A YOUNG PATIENT MANIFEST-
ING ALSO ARTERIAL HYPERTENSION
AND HYPERTHYROIDISM*

With Comments on the Newer Studies of the Etiology and the Therapy of Multiple Sclerosis

By LEWELLYS F. BARKER, M.D., LL.D.

Baltimore

When a patient presents symptoms and signs that point to multiple lesions within the central nervous system, it may be easier to decide upon the site of the lesions than to be sure as to their nature. The differentiation of the various maladies that may lead to multiple lesions within the central nervous system may tax seriously one's powers of diagnosis. Indeed, in some cases, one has to be content with a probable diagnosis rather than with certainty.

The patient selected by Doctor Pincoffs for the clinic today exhibits phenomena that might, on first consideration, be variously interpreted; but, after full consideration, with careful weighing of the evidence, it is possible, I believe, to arrive at diagnostic conclusions that leave but little, if any, doubt as to the nature of the main malady. The principal data regarding the history of the patient have been summarized for me by Doctor Miles of the Resident Staff.

CLINICAL HISTORY

The patient, Barbara B., a white woman, aged thirty-one, unmarried, was admitted to Ward A of the hospital of the University of Maryland, in the service of Dr. H. M. Stein, on November 1, 1930. Her *chief complaints* were of stiffness, weakness, and numbness in the lower extremities and back, occasional loss of bladder control, tremor of the hands, and disturbance of vision.

* Clinic to Physicians at the University of Maryland, Thursday, December 4, 1930.

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Professor Barker's University of Maryland Clinics

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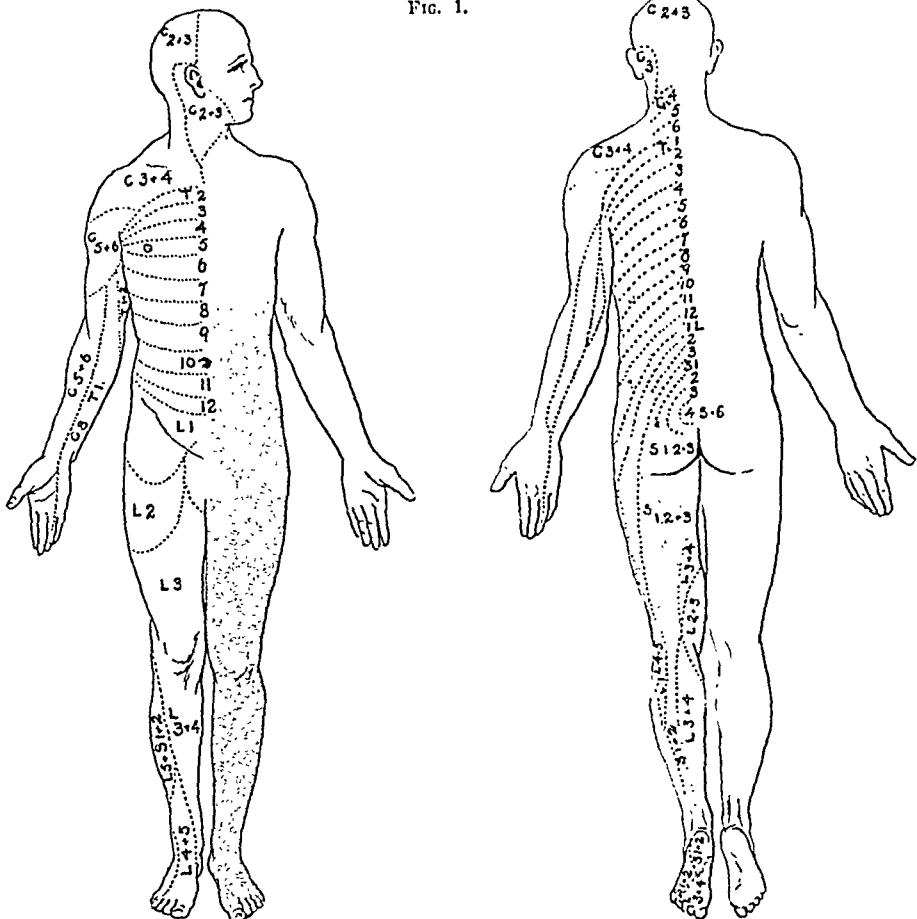
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Later in the summer, the legs became still stiffer and, when she lay on her back, she experienced great difficulty in assuming the sitting posture. Two months before admission to the University Hospital here, she began to suffer at times from loss of sphincter control, both bowel and bladder being affected; she said that she had great difficulty in retaining the urine and faeces until a bedpan was brought to her. The upper extremities have not been involved at any time except perhaps for a little numbness of the hands. She has had no pain. She has noticed, however, that she had a tendency to "lose the sense of the position of her legs in bed."

During the course of the illness, her appetite has remained good, she has lost no weight, and she has been mentally clear and cheerful.

Inquiries regarding her *past history* showed that she had always enjoyed

FIG. 1.



Shaded area indicates area of obtunded pain sensation, found on examination shortly after the patient entered the hospital, about a month before this clinic was held.

excellent health except for (1) occasional headaches, (2) a little leucorrhea at one time, and (3) transitory pains in the knees that suggested rheumatism.

The *family history* throws no light upon the case.

On *physical examination* upon admission to this hospital, she was found to have: slight fever; a pulse rate that varied from 90 to 110; and blood-pressure of 210 systolic, 120 diastolic, which fell later to 164 systolic and 100 diastolic. Nothing abnormal could be detected in the lungs, heart or abdomen. No foci of infection could be discovered, the oral sepsis having been removed through extraction of all the teeth. The tonsils were small and did not seem to be infected, and there was no evidence of infection of the paranasal sinuses or of the pelvic organs.

On *neurological examination*, there was outspoken spastic paraplegia of the lower extremities, with marked increase of the deep reflexes, bilateral ankle clonus, and a positive Babinski on both sides. The pathological reflexes were somewhat more marked in the left lower extremity than in the right. The spasticity included the abdominal muscles and the muscles of the lower back. There was moderate diminution of sensibility for all modalities in both lower extremities on entrance, but the sensibility has improved somewhat during her stay, though some obtunding of the pain sense has continued to be demonstrable over the entire left lower extremity and over the left side of the trunk, in front and behind, as high as the level of the eighth or ninth thoracic segment (Fig. 1). Deep sensibility was lost in both lower extremities; the patient could detect neither the direction nor the extent of passive movements of the great toe on either foot and there was loss of vibratory sense over the bony prominences of the ankles, the knees, and the crests of the iliac bones. The nerve head in the left eye was found to be somewhat lighter in color than that in the right eye (partial optic atrophy). In the left eye there was also a small pigmented area, about $1\frac{1}{2}$ nerve-head diameters in size, situated on the nasal side; there seemed also to be a slight increase in the light streak and the vessels in that eye were smaller than normal. Charts of the visual fields, however, revealed no definite restriction, though the patient stated that people looked rather pale to her and that "the trees did not seem so green as usual." On attempting the finger-nose test, there was marked intention tremor on both sides.

Laboratory Findings.—*Blood.*—Though there was a definite secondary anemia when the patient was studied at the Johns Hopkins Hospital at the end of June, the red count here in the hospital has been somewhat above normal, the counts varying between 5,200,000 and 5,800,000 R. B. C., and the hemoglobin percentage has been usually about 100. The leucocyte count has varied between 6,200 and 9,500, with 72 per cent. of polymorphonuclears. The Wassermann reaction was negative. The non-protein nitrogen content of the blood was 27 to 29 milligrams per cent., the sugar content 75 to 78, the chlorids 220, and the carbon dioxid combining power 62.

The *stomach contents* contained 45 acidity per cent. of free hydrochloric acid and 57 acidity per cent. total acidity.

The *urine* varied in specific gravity between 1020 and 1030. The tests for albumin, sugar and casts were always negative. The phthalein output was 60 per cent. in two hours and the concentration and dilution tests yielded normal results.

The *cerebrospinal fluid* yielded negative findings and Queckenstedt's test

was negative, showing that there was no obstruction in the spinal subarachnoid space.

The basal metabolic rate on November 6th was 25 per cent. plus, on November 12th, 19 per cent. plus, on November 29th, 42 per cent. plus, though just before this third reading was made the patient had had lumbar puncture done and had been taking strychnin.

Roentgenograms of the spine and of the paranasal sinuses were negative.

Course in the Hospital.—Careful observation during the past month has revealed no nystagmus and no scanning speech, the blood-pressure has fallen somewhat, and the pulse rate has varied, though it has always been somewhat accelerated; repeated examinations of the urine have been negative for albumin and casts. The general condition has remained good and she has lost no weight. She has regained much of the power to move the legs, though the left leg has remained spastic. The area of obtunded pain sensation first found seems to have largely cleared up, though pain sensation is still somewhat dulled over the soles of both feet.

DISCUSSION OF THE DIAGNOSIS

The accelerated basal metabolic rate, together with the tachycardia, is strongly suggestive of some overactivity of the thyroid gland, though there are no marked eye signs and the thyroid is only slightly enlarged, if at all. Though the blood-pressure has oscillated somewhat, it has been continuously much above normal. Since no signs of renal disease could be made out, all renal function tests having yielded findings within normal limits, the arterial hypertension has been believed to be of the so-called "essential" type, though a possible relation to the hyperthyroidism, on the one hand, and to the mild recurring headaches (possibility of migraine), on the other, has been kept in mind. The main diagnostic interest has centered in *the disease of the nervous system*. There has, of course, been no doubt that organic lesions exist; a functional malady could not account for the neurological symptoms and signs. As to the *localization of the lesions* within the central nervous system, the spastic paraplegia and the disturbances of sensibility point to an extensive lesion of the spinal cord at the level of the eighth or ninth thoracic segment, with involvement of the lateral funiculi on both sides (more marked on the left than on the right), of both dorsal funiculi (because of the loss of deep sensation) and, to a lesser extent, of Gowers' tract in the ventrolateral fasciculi on both sides, but more marked upon the right side than upon the left, because of the greater disturbances of sensibility in the left lower extremity than in the right. The visual disturbances point to retrobulbar in-

volvement of the left optic nerve. The intention tremor is suggestive of some lesion in the brain stem. The loss of abdominal reflexes could be due to the lesion in the spinal cord or to lesions still higher up. The sphincter disturbances must also be of spinal-cord origin.

We have evidence then of *multiple lesions* within the central nervous system. You will recall that the optic nerve is a part of the central nervous system. We have, therefore, to deal with *disseminated lesions in the brain and in the spinal cord*; the two principal lesions would seem to be (1) in the left optic nerve and (2) in the spinal cord at the level of the eighth or ninth thoracic segment.

We have next to consider the *nature of the neurological lesions*. On account of the oscillation of the symptoms, *cerebrospinal lues* was at first thought of, but this was quickly ruled out by the negative findings in the cerebrospinal fluid and by the negative Wassermann reaction in the blood. On account of the fever, which, though slight, has persisted under observation, a *disseminated encephalomyelitis* has been kept in mind as a possibility, but the picture has not been that of a lethargic encephalitis, nor does it seem likely that we have to deal with any other form of encephalomyelitis with disseminated lesions.

The occurrence of spastic paraplegia with loss of abdominal reflexes and with visual disturbances in a young person makes one think at once of *disseminated nodular sclerosis* (*multiple sclerosis*), and further evidence of the validity of this diagnosis is to be found in the intention tremor and in the marked oscillation in the symptoms. It is uncommon to have as marked a febrile reaction as we see in this patient in ordinary multiple sclerosis, and the eye findings have been somewhat atypical, since the commonest finding in disseminated sclerosis is bilateral temporal pallor of the discs, whereas here we have had to deal with a unilateral optic neuritis which has receded.

Certain other possibilities have not been overlooked. Thus, the existence of rather marked arterial hypertension in association with some narrowing of the retinal arterioles, made one think of the possibility of an *arteriosclerosis of the central nervous system*, but there is much against this diagnosis, for, in the first place, the onset of the symptoms referable to the spinal cord was gradual and has been

characterized by exacerbations and remissions, scarcely compatible with the view that the spinal cord lesion was due to a sudden softening of the thoracic cord from occlusion of a vessel, even though the severe oral sepsis that preceded was compatible with the idea of a localized thrombosis in the cord. The age of the patient is, too, against the idea of any extensive central arteriosclerosis.

The close relation of the onset of the symptoms to the trauma experienced when the patient wrenched her back on the stairs, made one think of a possible *bony lesion of the spine*, but this has been ruled out by X-ray examination.

Tumor within the spinal canal seems to be ruled out by the negative Queckenstedt's test and by the improvement of the symptoms in the hospital. Against the diagnosis of tumor also should be mentioned the coëxistence of visual disturbances and of intention tremor with the spastic paraplegia.

We seem, therefore, justified in making the diagnosis of disseminated nodular sclerosis with considerable certainty.

As our knowledge concerning disseminated sclerosis has grown, the diagnosis has come to be made at much earlier stages than formerly. The triad of symptoms—nystagmus, scanning speech, and intention tremor—that Charcot described, occurs only in advanced stages of the disease. Among the early symptoms most often met with are: (1) loss of the abdominal reflexes, (2) weakness of the abdominal muscles, and (3) bilateral temporal pallor of the optic discs. In very many cases, the initial symptoms are those of spastic paraparesis, and many of the cases formerly diagnosed as transverse myelitis or as lateral sclerosis are now known to have been, in reality, cases of disseminated nodular sclerosis. Spastic paraplegia, occurring in a young person, let me emphasize again, will, in a very large number of the cases, be found on careful study to be due to multiple sclerosis.

PATHOLOGICAL ANATOMY OF MULTIPLE SCLEROSIS

It is interesting that one of the first recorded observations of the lesions of multiple sclerosis was that made by Carswell, a medical student in London. As he accompanied visiting physicians about the hospital and in the postmortem room, he requested (and received) permission to draw, in colors, the pathological tissues that

were exhibited to the students. Among his sketches is one made in 1837 in which superficial colored plaques were found to be scattered through the spinal cord and the medulla oblongata. About the same time, perhaps even a little earlier, Cruveilhier, described a similar pathological condition, which he designated as a "grave degeneration." He stated that the new tissue was dense, much more dense than the cord itself, and "not comparable to any other morbid tissue that he had ever seen." Cruveilhier called the condition *induration of the cord with paraplegia*, and in France the malady has ever since been known as "Cruveilhier's disease."

During the past one hundred years, many neuropathologists have busied themselves with careful studies of the gross and microscopic lesions of this remarkable malady. The distribution of the lesions is very irregular, but certain parts of the central nervous system show an especial predilection for them, namely, the brain stem, the corpus callosum, the walls of the lateral ventricles, the floor of the fourth ventricle, the pons, the cerebral peduncles, the medulla oblongata, and the white substance of the brain and the spinal cord. The optic nerve and tracts are frequently involved, much more often than the olfactory, the trigeminal or the hypoglossal nerves. The peripheral nerves elsewhere are almost never involved.

Histological studies of the lesions have made great progress, thanks to the newer methods of staining. The most interesting histological fact is that, in early lesions, it is the myelin sheaths that disintegrate, whereas the axis cylinders may remain intact. In later lesions, there is marked proliferation of the glia. It seems probable that the discordance between the clinical symptoms and the gross pathologic lesions is due, in the main, to this preservation of the axis cylinders. If one examines, with the naked eye, the brain and spinal cord of a patient dead of multiple sclerosis, he cannot help but wonder why clinical symptoms have not been more pronounced than they were observed to be during life. Moreover, the remission of the symptoms so frequently met with seems to be due to varying pressure upon axis cylinders by the degenerative products of the myelin sheaths. Symptoms like nystagmus, intention tremor, and scanning speech are also probably to be explained by irregularity in the conduction of impulses through the axones because of the myelin sheath degeneration; instead of a steady transmission of

the impulses through the axis cylinders, the flow may be interrupted, much as a stream of water from a tap can, by gradually turning the tap, be changed to a series of drops.

Certain special elective methods of staining have been most helpful in unraveling the details of the lesions. Thus, with Weigert's method, the areas in which the myelin sheaths have been lost are easily demonstrable. The absence of descending and ascending degeneration of any high degree, as revealed by Marchi's method, is probably due (1) to the fact that the axis cylinders persist (as shown by Bielschowsky's silver method), and (2) to the additional fact that the nerve cells that give off the axones are not, as a rule, degenerated (Nissl's methylene-blue method). All these staining methods, taken together, reveal the character of the lesions in a way that could not be discovered by any single technical procedure.

Interesting changes have been found, too, in the sheaths of the blood-vessels in the regions in which the lesions occur; thus lymphocytes, plasma cells, and polyblasts are abundant there, and remind one of the findings found in dementia paralytica and in certain trypanosome invasions. Déjerine and Marie thought that the vascular lesions were primary, but Dawson maintains that the first injury is to the myelin sheaths, the vascular lesions appearing later.

ETIOLOGY OF DISSEMINATED SCLEROSIS

The cause of this remarkable malady has long been a mystery. It was thought by many that the lesions were of an inflammatory nature and that the gliosis was secondary. Later studies showed that the lesions were more often degenerative than inflammatory at first. Some have maintained that the gliosis is primary and that the degeneration of the myelin sheaths is secondary. Those who have supported this view have thought of the possibility of a congenital gliosis. The distribution of the lesions in relation to the changes in the blood-vessels has made others think of a vascular origin of the disease or, at any rate, of an origin through something brought to the nervous tissue by the blood-vessels.

As etiological factors, climate, heredity, physical and psychical traumata have been suggested; they may play a part as predisposing factors, but some single specific etiological agent, micro-organismal or toxic seems probable.

The frequency of the onset of symptoms after infectious diseases of various sorts soon led to the idea of an infectious or toxic origin for the disease, but inasmuch as the nature of the preceding infection varied so greatly, it was assumed for a time that disseminated sclerosis might be due to localization within the nervous system of any one of the causative agents of a whole series of infectious diseases. Still others assumed that the infective agent, itself, did not reach the nervous system, but that the foci of sclerosis were due to localized intoxications within the central nervous system. This latter view has not appealed, however, to many pathologists, since the focal distribution is much more strongly suggestive of the actual localization of some infective micro-organism at the site of the lesions, leading to the secondary changes about it.

The foci that occur in isolated fashion and successively over a long period of time could scarcely be due to intoxication but must be due to some living germ. In addition to the disseminated foci, however, there is some diffuse sclerosis beneath the pia mater and in the walls of the ventricles and it is possible that this diffuse sclerosis could be due to toxic action.

Many attempts have been made to reproduce the disease experimentally in animals. In 1913, W. Bullock inoculated a rabbit with the cerebrospinal fluid from a patient suffering from disseminated sclerosis and on the third day, the animal exhibited a quadriplegia. Again, during the World War, Steiner and Kuhn made injections of animals in a similar way and reported the discovery of spirochetes in the blood of these animals. They drew the conclusion that disseminated sclerosis is a spirochetal disease and that it is, possibly, transmitted by insects, especially by ticks. They even gave a name to the micro-organism, calling it *Spirocheta argentinensis*.

In 1919, Marinesco, working at the Pasteur Institute in Paris, with materials derived from patients suffering from disseminated sclerosis, produced paralysis in guinea pigs and found spirochetes that exhibited rapid movement. Schuster, later, by means of silver staining and the use of the ultra-microscope, also found what he believed to be spirochetes.

Attempts to corroborate these spirochetal findings have not been very successful, though, until recently, the possibility of a spirochetal

origin of disseminated sclerosis seemed to be the only clue to infectious etiology obtained. In 1923, Noguchi, of the Rockefeller Institute for Medical Research, sounded the deathknell of the theory of spirochetal origin. With a faultless technic and with his wide experience in the study of the spirochetal diseases, he was able to assert positively that spirochetes cannot be demonstrated on attempts at experimental transmission of the disease to animals.

During the present year, 1930, some observations have been published, which, if they should be verified by others, promise to throw an entirely new light upon the etiology of this remarkable disease. Miss Kathleen Chevassut, working in the pathological laboratories of the Westminster Hospital in London, after careful studies of the "gold curve" in the cerebrospinal fluid, made cultures from the spinal fluid of human beings in whom the symptoms of disseminated sclerosis were developing. Using a mixture of Hartley's broth and normal human serum, as a culture medium, she believed that she proved that, if a living virus were present, it is not demonstrable by ordinary bacteriological methods. She obtained, making use of Beck's massive microscope with special objective and illuminator and a mercury vapor lamp, groups of characteristic colonies of spherical bodies, and believed that these were micro-organisms belonging to the group of the filtrable viruses. Sometimes small refractile granules were attached to the spherules, one or more upon a single sphere; she could watch the granule move away from the sphere and occasionally a fine filament between a granule and a sphere could be seen. These spherical bodies were grown from the cerebrospinal fluid of 176 out of 188 cases, though they could never be recovered from controls; the investigator, therefore, concluded that she was dealing with the specific pathogenic agent concerned in disseminated sclerosis. This virus, designated *Spherula insularis*, resembled in many respects the virus of bovine pleuro-pneumonia, which is regarded as a sort of connecting link between ordinary bacteria and the filtrable viruses.

It is interesting that, for the culture medium, healthy human serum must always be used, for if she used the serum from a patient suffering from multiple sclerosis, there was no growth. Moreover, the exact degree of P content of the medium seemed to be important (not greater than 7.6 nor less than 7.5). The growth

of spherical bodies was obtained under aërobic conditions, the cerebrospinal fluid being received directly into the medium. Attempts were made to determine whether the spheres and granules represent stages in the life cycle of a virus. In experiments on ultrafiltration, she used collodion membranes with a known size of pore (Elford's technic).

Hicks undertook experiments upon monkeys, injecting the Chevassut virus intravenously in some and into the cisterna magna in others. In two out of seven monkeys injected, clinical symptoms developed and certain lesions of the central nervous system not unlike those of multiple sclerosis were demonstrable at autopsy. In one monkey, the virus was obtained from the cerebrospinal fluid one month after the injection; nine months after injection, there was a transitory paralysis of the posterior extremities, and fourteen months after injection, the anterior extremities became paralyzed also. The animal was then killed and two foci of degeneration were found (by Marchi's method), one in the left dorsolateral region and one in the right lateral region of the spinal cord. The blood-vessels in the lesions showed cell infiltrations similar to those of human multiple sclerosis. The second monkey lived for seven months after inoculation; the virus was recovered from the cerebrospinal fluid during life and, at autopsy, there was degeneration at the periphery of the ventrolateral columns and small foci were disseminated through both lateral funiculi.

The English investigators further found that if the specific virus were killed, the fluid containing it might be injected into the veins of an animal without causing any special harm.

TREATMENT OF MULTIPLE SCLEROSIS

Until very recently, the treatment of disseminated sclerosis has been very unsatisfactory. One had to depend upon rest, general upbuilding, and symptomatic treatment.

After the spirochetal theory had been advanced, attempts were made to cure the disease by neosalvarsan, by germanin (Bayer 205), and by other spirocheticidal agents, but no one obtained results that were particularly promising.

Since the reported discovery, in London, of an ultramicroscopic virus, attempts have been made by Sir James Purves-Stewart and

his associates, (1) to secure an immunizing serum and (2) to develop a method of vaccination. Some 128 patients have been treated by an autogenous vaccine and seventy of these have been under observation long enough to permit of a judgment as to the effects. The disease seems to have been totally arrested in eight cases and the cerebrospinal fluid has become sterile. In thirty-two of the patients the condition was ameliorated and there was no more progression, but the cerebrospinal fluid remained virulent. In thirty of the patients, no beneficial influence could be detected. Keeping in mind the dangers of drawing conclusions regarding any forms of therapy in disseminated sclerosis (because of the remissions of the disease that occur spontaneously), it must be admitted that these results are really encouraging and the method should be given further trial. I am told that Dr. Irving J. Spear is working here with the methods of the English investigators; perhaps it will be possible to apply them to the treatment of the patient before you.

I am passing around the articles in which the London studies are reported and also two very important discussions of the whole subject of multiple sclerosis, namely, that at the Association for Research in Nervous and Mental Diseases in New York in 1922, and that of the Annual International Meeting of the Paris Neurological Society in 1924. Perusal of these articles at your leisure will put you in touch with the principal known facts concerning multiple sclerosis.

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ON A FORM OF RICKETS OCCURRING IN ASSOCIATION
WITH SPORADIC CRETINISM; INTERMITTENCY
OF BONY GROWTH MANIFEST IN TRANSVERSE
LINES IN ROENTGENOGRAMS OF LOWER
ENDS OF FEMORA; DEVELOPMENT
OF OUR KNOWLEDGE OF
"BOTTLED LIGHT"*

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A SURVEY of the advances made in the many fields of medicine during our time will quickly convince anyone that the progress made in the study of the internal secretions, on the one hand, and in that of dietetic insufficiencies on the other, has been outstanding. In the patient selected by Professor Pincoffs for our clinic today, we have apparently to deal both with an endocrine deficiency and with a vitamin deficiency. These two forms of deficiency occurring in one and the same patient will afford opportunity for discussion of some of the newer facts that have been accumulated bearing upon the particular endocrine lack and the particular vitamin lack in evidence here.

First, let me give you an epitome of the clinical history as compiled for me by Dr. John Lynn of the Resident Staff.

CLINICAL HISTORY

The patient, M. B., a white male child, two years of age, was re-admitted to the University Hospital on December 4, 1930, entering Ward G in the service of Dr. C. Loring Joslin. In the entrance note, made by Dr. E. S. Brown, it was stated that "the patient was brought for the purpose of further study, and especially for comparison with his condition when studied a year earlier in the same hospital, when a diagnosis of thyroid insufficiency was made."

Family History.—The child's mother is markedly obese, as are all the relatives on the maternal side. The parents have had four children in all, the patient being the third. The other three children are said to be normal in all respects.

Studies of the mother at the Johns Hopkins Hospital have shown her to

* Thursday Clinic to Physicians at the University of Maryland Clinical School, December 11, 1930.

be an obese, hysterical white woman, unstable, unreliable, of immature personality and with many somatic complaints without adequate organic basis. She is described as "a chronic sympathy seeker." Her constitutional difficulties have been accentuated by her marital situation, inasmuch as it is reported that her Italian husband has not only shown lack of tenderness for her but has abused her and has sometimes even beaten her.

Prenatal Record.—The child's mother remained in bed for the last three months of her pregnancy. Though she complained of various symptoms and of being abused by her husband, the physicians at the Johns Hopkins Hospital could find no organic explanation for her invalidism. The mother still claims that she was in poor health during the entire period of the pregnancy and she blames the condition of her child upon the mal-treatment she suffered from her husband.

Delivery Record.—Delivery spontaneous; seven-pound male child, full term, normal appearance; some delay in crying, requiring stimulation over several minutes.

Previous History.—Breast feeding for nine months, without difficulties or digestive disturbances. Ever since birth, there have been frequent "spells" of dyspnea, lasting from three to four minutes, accompanied by cyanosis of the hands and feet; some of the attacks lasted for several hours. The cry has always been hoarse. The mental development has obviously been retarded. Up to the end of the first year, the child remained dull, lethargic and unresponsive and he took very little interest in his surroundings; the teeth failed to erupt at the normal time. Bodily growth was markedly retarded.

Hospital Record in 1929.—On October 11, 1929, the patient was admitted with a temperature of 101.4°, respiration 35, pulse 130, and with the complaint of cough and of cold in the chest.

On physical examination at that time, the child was found to be slightly obese, generally under-developed, length 27½ inches, weight 18½ pounds, maximal circumference of head 18 3/4 inches, maximal circumference of chest 19 inches. The expression was dull and lethargic, suggesting mental deficiency, and there was failure to react adequately to stimuli. The child was unable to sit up, or to reach for objects. Inspiratory dyspnea, cry hoarse, lips pseudo-edematous, cheeks boggy and thick, skin coarse, dry and boggy, with excess of subcutaneous fat.

Head square and large, left parietal boss more prominent than right, anterior fontanelle admitted three fingers and measured 2 inches across. Posterior fontanelle closed. Hair dry and sparse. Narrow lid slits. Broad nose, with flat bridge; mucopurulent nasal discharge. Lips thick. Child drools. Tongue large and protruding. No teeth erupted. Pharynx injected. Neck short and thick. Thyroid not palpable. Signs of acute bronchitis and bronchopneumonia in the chest. Umbilical hernia. Hands and feet flat, square, stubby looking. Epiphyses of long bones slightly enlarged. Moderate bowing of tibiae. Reflexes normal.

On laboratory examination, there was a marked secondary anemia, red blood cells 3,390,000, hemoglobin 75 per cent., with a moderate leucocytosis (14,600).

On X-ray examination, there was marked delay in the ossification of the epiphyses of the long bones.

The diagnoses, recorded at the time, include (1) acute bronchitis and

bronchopneumonia, (2) rhinopharyngitis, (3) sporadic cretinism, with umbilical hernia, and (4) rickets.

During the child's stay in the hospital, the infections of the inspiratory tract cleared up, but two abscesses formed under the scalp and had to be incised one month after admission; the pus contained streptococci and pneumococci. Toward the end of his stay, there was a recurrence of the nasopharyngitis, with slight fever and tachycardia.

The hypothyroidism was treated with thyroid extract, beginning with $1/20$ of a grain twice a day, the dose being gradually increased to $1/5$ of a grain twice a day on discharge.

Under thyroid treatment, the clinical improvement was rapid and marked. The child became mentally alert, responded quickly to stimuli, was physically active, and could even stand in his crib with the aid of some support. The tone of the musculature improved, the child looked less pudgy, and the skin became less dry. The attacks of dyspnea and cyanosis disappeared, though the voice still remained hoarse.

Interval History.—The child left the hospital on December 14, 1929, but has been under observation in the out-patient department, from time to time, ever since. During this interval, several head colds have been treated, as well as two gastro-intestinal upsets with diarrhea.

For several months the child received $1/10$ grain thyroid twice daily, but this was later increased to $1/4$ grain twice daily.

The gain in weight and height has been fairly rapid, the height increasing from $27\frac{1}{2}$ inches at the age of one year to 32 inches at the age of two years, and the weight from $21\frac{1}{2}$ to 28 pounds. The general appearance of the child has gradually improved under the thyroid therapy. The dry, thickened skin, the swelling of the lips and tongue, and the sluggishness of general and of mental activity have all been benefited, though the child still lags far behind the pace set by the mother's other children at the same age. The cry has continued to be hoarse.

This child crawled first at the age of one year. The first teeth (lower incisors) did not appear until the nineteenth month. During the past five months, the child has finished cutting the first molars; he now has six teeth below and four above. During the two months before admission, the child became able to pull himself into an erect position by taking hold of a chair or the edge of a bed, and he has also begun to enunciate simple words such as "da-da." It is said that he can point to different members of the family correctly when they are named. During the last few weeks before admission, he had taken a few steps with the aid of some support.

Present Condition.—Certain residuals of the hypothyroid physical condition are still in evidence in the dwarfism, the puffy, expressionless face, the awkwardness of movement, the dryness of the skin and hair, the narrow lid slits, and thickened eyelids, the configuration of the feet and hands, and the umbilical hernia.

The circumference of the chest at the nipple level is now $21\frac{1}{2}$ inches. The maximal circumference of the abdomen is $19\frac{1}{2}$ inches. The distance from the umbilicus to the crown of the head is 17 inches; from the umbilicus to the sole of the feet 15 inches; total length 32 inches.

The physical examination still reveals signs of rickets in the open anterior

fontanelle, the prominent bosses on the skull, the slight rickety rosary, and the slight symmetrical epiphyseal enlargement at the wrists.

Laboratory Tests.—Blood: red blood cells 3,990,000, hemoglobin 72 per cent. white blood cells 9,000; differential count: polymorphonuclears 28.7, eosinophiles 3.2, small mononuclears 56, large mononuclears and transitionals 2.75; Wassermann negative. Blood sugar 74, serum calcium 10.26 (normal 10 milligrams per cent.), serum phosphate 4.5 (normal 5 milligrams per cent.). Urine and faeces negative. Basal metabolic rate (under morphine) on three different occasions, minus 16, minus 17, and minus 22 per cent.

X-Ray Examinations (Dr. A. J. Walton).—*Skull.*: Unusual thickening of flat bones; posterior fontanelle entirely closed; anterior fontanelle open; tendency toward separation of the frontoparietal and parietal occipital sutures; sella moderately large; sphenoidal sinuses not developed.

Thorax and Shoulders.—Underdevelopment of heads of humeri; small bilateral cervical ribs; non-union of laminae of thoracic and lower cervical vertebrae; marked blunting of anterior ends of ribs at costochondral junction, suggestive of rickets.

Pelvis.—Wide separation between ilia and ischia and between descending ramus and ascending ramus; epiphyses of femora not visible, indicating marked retardation of the ossification process.

Right Wrist and Hand.—Beginning ossification of os magnum but no other centers of ossification visible in carpal bones (at two years of age, there should be at least two visible).

Right Ankle and Foot.—Three centers of ossification visible (astragalus, os calcis, and cuboid).

Psychiatric Report (Dr. Alice J. Rockwell).—According to Kuhlman revision of the Binet-Simon test, the patient passes all tests for six months but none for the one-year level. The actual performance level is, therefore, under one year.

Nose and Throat Report (Dr. A. Jaffe).—Injection of pharyngeal vault; slight mucoid posterior nasal discharge; right ear-drum opaque and bulging; left ear-drum injected but not bulging. Impression: Rhinopharyngitis and bilateral otitis.

Diagnosis.—The following diagnostic conclusions seem justified:

1. Infantile hypothyroidism (sporadic cretinism) with retarded physical and mental development.
2. Rachitis.
3. Rhinopharyngitis and bilateral otitis media.
4. Secondary anemia.

DISCUSSION OF THE HYPOTHYROIDISM

Sporadic cretinism differs somewhat from the endemic forms of cretinism that are met with in the valleys of the Alps and other regions.

Sporadic cretinism (or congenital hypothyroidism) is far less rare than most people imagine. One may meet with it in various degrees; in the milder forms, the deviations from the normal might

not strike the casual observer. The importance of early diagnosis, however, cannot be overestimated, since delay in the institution of thyroid treatment seriously menaces the future welfare of the child.

Our patient, though born at full term, was not preternaturally large. I mention this, since babies that are unusually large at birth, weighing ten pounds or more, should make one suspicious of prenatal deficiency of the thyroid.

The appearances of our patient when studied one year ago were very characteristic of infantile hypothyroidism. The delayed physical and mental development, the short, stubby hands and feet, the obesity and general pudginess of the body, the narrow lid slits and thickened eyelids, the thick lips and tongue with drooling, the delayed dentition, the swollen abdomen with umbilical hernia, and the absence of palpable thyroid, were all characteristic of the condition. The roentgenograms made one year ago and at the present admission show delay of the appearance of ossification centers and marked retardation of bony growth.

The diagnosis of hypothyroidism was corroborated by the therapeutic tests. Under suitable doses of thyroid extract, the child's physical condition began rapidly to improve and the mental state quickly altered for the better. Under supervision in the out-patient department, the dosage of thyroid extract was increased gradually in order to avoid the production of toxic symptoms, for when one is treating such a child, one wants to be on the lookout for restlessness, sweating, insomnia, diarrhea, tachycardia, loss of weight, or fatigability. The child should be seen frequently enough to permit of adequate control of dosage of thyroid extract. Should toxic symptoms appear, the dose must be reduced immediately, or the thyroid substance left off entirely for a time, after which a smaller dosage than that which produced toxic symptoms can be administered again.

I have been very much interested in the roentgenograms of the skeleton in this child. The delay in the appearance of the centers of ossification is very striking, and the great masses of cartilage not yet ossified is a characteristic appearance.

The marked inhibition of the longitudinal growth of the bones and of the epiphyses, with less inhibition of the growth of the breadth of the bones is also a striking feature.

In cretins, there are often permanent changes in the hip-joints

and X-ray plates are suggestive of the so-called Legge's disease or Calve-Perthe's disease; but the latter is a primary necrosis of the epiphysis of the femur and is an entirely different disease from that met with in cretins, for here we have to deal rather with a disturbance of the ossification of the head of the femur and, later on, we may expect irregular and incomplete replacements of the cartilage by bone.

On examining the X-rays of the bones in this case, I was very much struck by the *series of transverse lines* observable at the lower end of the femur on both sides, lines that run parallel to one another and that lie at variable distances from one another and from the end of the bone (Figs. 1 and 2). On close examination, somewhat similar lines can be seen in the iliac bones, at their upper part. Knowing that Dr. E. A. Park had been greatly interested in changes in the bones in infants, I showed him the plates and he called my attention to a paper he had published (in association with Miss Eliot and Miss Souther) on transverse lines in X-ray plates of the long bones of children, in which the origin of these lines is attributed to peculiar alterations in bony growth. He also showed me this extraordinarily interesting article by Goetzky and Weihe, in which these parallel lines are reported, in 1914, in roentgenograms of a child suffering from myxedema. The extraordinary development of these lines is well shown in their figures 2, 3, 4. They compare these lines to the rings of periodic growth on cross-section of a tree and assume that they are the results of periodic functional disturbances of the thyroid, leading to periodic arrests of growth. It seems obvious that in our patient, too, there have been such pauses of growth during the last year.

I am throwing on the screen, a photograph (Fig. 2) of our patient taken recently (unfortunately, no photograph has been kept of the child when first seen a year ago) and I am projecting some other pictures of cretins observed elsewhere. (Figs. 4 and 5.) Once one has seen the general physical appearance of an outspoken cretin, he is not likely to overlook it afterward and acquaintance with the severer forms is helpful in the recognition of the forms transitional from these to normal appearance.

Endemic cretinism is, as I have said, certainly somewhat different from sporadic cretinism such as we deal with here. Endemic

cretinism is associated geographically with endemic goiter. In endemic cretinism, there is always hypothyroidism, but not all of the manifestations can be explained by the thyroid insufficiency. Congenital sporadic myxedema is believed to be teratological in origin and is associated with total or partial absence of the thyroid (including the lingual thyroid); in other words it is an athyreosis or a hypothyreosis, whereas in endemic cretins, we deal with a peculiar form of thyroid atrophy, confined to a certain geographical distribution. Not all endemic cretins have goiter, though both goitrous and non-goitrous endemic cretins show the peculiar atrophy of the thyroid tissue. The mental deficiency of the endemic cretin is different from that of ordinary imbecility or idiocy, for the personality of the cretin is better preserved; he has greater faculties of reflection and is generally optimistic and happy, and his memory remains fairly good. His mentality, however, always remains like that of a child, for the development of his brain, like that of his bony system, has undergone irremediable retardation. There is often, too, marked disparity between the physical signs and the mental changes in the endemic cretin.

On the whole, there are quite marked differences between the endemic cretins and the sporadic cretins, for in the latter, the clinical picture is more uniform, the personality is less marked, the dwarfism is more pronounced, and the myxedema is more constant, whereas, in endemic cretinism, the personality is more marked and more varied, and myxedema is less constant (De Quervain).

The goiter of the endemic cretin is not a colloid goiter; the characteristic of the cretinous goiter is a peculiar atrophy of parts of the thyroid tissue. The thyroid contains relatively little iodine and the iodine content of the blood is only about 50 per cent. of the normal. It would seem that the epithelial cells of the endemic cretin's thyroid are incapable of fixing iodine and of using it physiologically. The normal content of the blood in iodine is from 8 to 13 thousandths of a milligram per 100 cubic centimeters of serum. The swinging gait of the cretin depends upon the changes in the head of the femur (so-called dissecting osteochondritis of the condyles) already referred to. Whether lack of iodine in the food is the cause of endemic cretinism has been much discussed. At any rate, the addition of sodium iodide to the cooking salt, so that 1/20

at a minimum, *per day* of iodine (and not more) is ingested, will go far toward preventing endemic cretinism.

Our patient is not an endemic cretin, but a sporadic cretin. He needs thyroid extract in sufficient doses to substitute for the deficiency in the thyroid activity of his aplastic gland. Under the treatment, if faithfully kept up, it is reasonable to expect a much greater restoration than could be looked forward to if the more serious condition of endemic cretinism existed. The thyroid treatment of infantile myxedema very quickly influences the specific changes in the soft parts and the ossification retardation favorably; the effect upon mental development is less prompt and less satisfactory.

I prefer at present to feed desiccated thyroid substance to patients with hypothyroidism in preference to administration of thyroxin, since the latter is only one of the substances of the thyroid among many doubtless that influence metabolism. Thyroxin is an iodized hydroxyphenylester of the amino-acid tyrosin, the molecule containing four atoms of iodine. The structure of the other iodine compounds in the thyroid is, as yet, entirely unknown to us. The remedies that influence rickets favorably will not replace thyroid preparations in the treatment of athyreosis.

IMPROVEMENT OF THE RACHITIS-LIKE CHANGES

When the patient was first seen one year ago, it was believed that he had rickets because of the square-shaped head with prominent parietal bosses, the wide-open fontanelle in front, the enlargements of the epiphyses of the long bones, and the moderate bowing of the fibulae.

At the present time the persistence of these changes, together with the presence of a slight rickety rosary and of suggestive X-ray changes in the bones, have corroborated the idea that rickets, or some disease simulating it, exists in this child.

Another strong support for the diagnosis of rickets lay in the following record of studies of the calcium and phosphorus content of the blood serum of the child. The calcium-content was found to be 10.27 and the inorganic-phosphorus-content was said to be between 2 and 3. Thus, though the calcium ^{of the} blood serum was reported to be within normal range,

FIG. 1



Roentgenogram of pelvis and lower extremities (at age of one year) before any treatment was given.

FIG. 2



Roentgenogram of pelvis and lower extremities after one year of treatment with thyroid and cod liver oil. The transverse lines at the lower end of the femora are well shown.

of a milligram per day of iodine (and not more) is ingested, will go far toward preventing endemic cretinism.

Our patient is not an endemic cretin, but a sporadic cretin. He needs thyroid extract in sufficient doses to substitute for the deficiency in the thyroid activity of his aplastic gland. Under the treatment, if faithfully kept up, it is reasonable to expect a much greater restitution than could be looked forward to if the more serious condition of endemic cretinism existed. The thyroid treatment of infantile myxedema very quickly influences the specific changes in the soft parts and the ossification retardation favorably; the effect upon mental development is less prompt and less satisfactory.

I prefer at present to feed desiccated thyroid substance to patients with hypothyroidism in preference to administration of thyroxin, since the latter is only one of the substances of the thyroid among many doubtless that influence metabolism. Thyroxin is an iodized hydroxyphenylester of the amino-acid tyrosin, the molecule containing four atoms of iodine. The structure of the other iodine compounds in the thyroid is, as yet, entirely unknown to us. The remedies that influence rickets favorably will not replace thyroid preparations in the treatment of athyreosis.

DISCUSSION OF THE RACHITIS-LIKE CHANGES

When the patient was first seen one year ago, it was believed that he had rickets because of the square-shaped head with prominent parietal bosses, the wide-open fontanelle in front, the enlargements of the extremities of the long bones, and the moderate bowing of the tibiae.

At the present time, the persistence of these changes, together with the presence of a slight rickety rosary and of suggestive X-ray changes in the bones, have corroborated the idea that rickets, or some disease simulating it, exists in this child.

Further strong support for the diagnosis of rickets lay in the first reports received of studies of the calcium- and phosphorus-content of the blood serum of the child. The calcium-content was said to be 10.25 and the inorganic-phosphorus-content was said to lie between 2 and 2.5. Thus, though the calcium-content of the blood serum was reported to be within normal limits, the phosphate-

FIG. 1



Roentgenogram of pelvis and lower extremities (at age of one year) before any treatment was given.

FIG. 2



Roentgenogram of pelvis and lower extremities after one year of treatment with thyroid and cod liver oil. The transverse lines at the lower end of the femora are well shown.

Fig. 3.

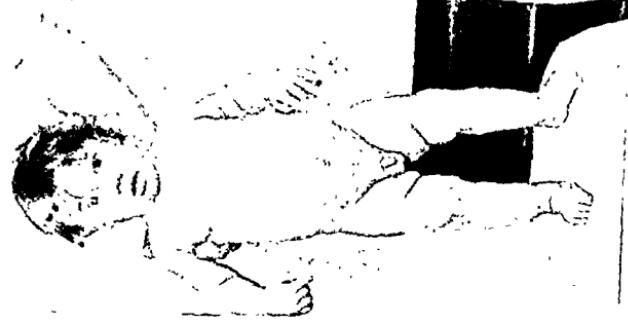


Fig. 4.



Fig. 5.



Cretin M. B. at the age of two years, after the institution of treatment by thyroid and cod liver oil.

Female cretin of same family.

A male cretin of Polish extraction whose family shows endogenous obesity.

content was reported to be enormously reduced (to practically one-half of normal). Such a hypophosphatemia has usually been regarded as characteristic of a florid rachitis, both in man and in experimental animals. On the other hand, against the idea of florid rickets, is the fact that the child has received daily from one to two drams of cod-liver oil, certainly during the past year and perhaps over a longer period. On account of the high degree of hypophosphatemia recorded, I asked for another determination, and today have received the report that the inorganic-phosphorus-content is now 4.5. I am inclined to believe that the low reading earlier made was due either to an error in technic or to a mistake in calculation.

Let us review very briefly the *development of our knowledge of rickets*, one of the most fascinating stories connected with the evolution of modern medicine. You will find it most elaborately told in this 214-page article by P. György, in volume 36, of the *Ergebnisse der inneren Medizin und Kinderheilkunde*.

Though the clinical picture of rickets has been very well known to medical men since the excellent descriptions by Glisson in 1650, our knowledge of the nature and pathogenesis of this malady has been more enriched by researches made during the past twelve years than by all the preceding studies through the centuries. We are still in the dark, it must be admitted, regarding certain features of the pathogenesis, but we may say that almost a complete triumph has been scored with regard to the practical side of the problem, namely, the treatment and prevention of rickets and allied states. For during the past few years, clinical observations have been supplemented by exhaustive X-ray studies, by chemical studies of intermediary metabolism, by accurate studies of the pathological histology of the disease, by experimental production of the disease in animals, and by studies of diet and of the effects of certain physical agents upon the malady; through a synthesis of all these studies, the very important practical results to which I have referred have been derived.

As a result of the newer studies, we are now able to give a better definition than ever before of what we mean by "rickets." Thus, on the *morphological* side, we have learned that the bony lesions are associated with increased formation of osteoid tissue that

remains uncalcified and that large areas of endochondrium, especially in the growing zones of bones, show delayed ossification. On the *chemical* side, we have learned that the body loses calcium and phosphorus, and, more particularly, that there is an altered distribution of calcium and of inorganic phosphorus in the blood serum. On the *etiological* side, we have come to realize the relation of the disease to lack of a protective substance and that this protective substance corresponds to vitamin D or to the action of certain light rays (in the ultraviolet). On the *therapeutic* side, we have learned that, by supplying either vitamin D, or light of a certain sort, in suitable amounts, ordinary rickets can be cured.

Whether or not inability of the intestinal wall to absorb calcium and phosphorus may play a part in the origin of rickets is still much discussed. Some would describe the disease as an "avitaminosis" (because of lack of vitamin D) or as an "anactinosis" (because of lack of the influence of certain light rays), but it must be remembered that the absence of vitamin D or absence of suitable light produces rickets only when the calcium and phosphorus in the foods are within the so-called rachitogenous zone. Moreover, vitamin D, since it occurs in yolk of egg, in fish, and in cod-liver oil, is not normally contained in the diet of the infant. Some authors, like Pfaundler, have, therefore, objected to the use of the term "avitaminosis," as well as of the term "anactinosis," as a designation of rickets, as these are both deficiencies of protective exogenous agents; he also objects to calling rickets an "aphylakinosis" (that is, a disease due to lack of protective substances of endogenous origin), but believes it due to a fault of constitutional make-up that determines mal-adaptation, perhaps a lack of some specific form of protoplasmic energy.

For the *diagnosis of rickets*, we depend (1) upon changes in the skeleton that can be recognized clinically, such as craniotabes, rickety rosary, enlargements of bones at wrists and ankles, abnormal grooves in the thorax, distortions of the pelvis, and curvatures of the long bones of the extremities, (2) upon roentgenograms that reveal (a) a diminished calcium content with reduction in the density of the shaft of the long bones, (b) changes at the junction of cartilage and shaft in the lines of calcification which look fringed, frazzled, or deckled rather than like even lines, (c) cupping and

flaring of the metaphyses (or beaker type of Göttsche); or the less severe change known as the cuff form of Göttsche, (d) an increased amount of osteoid tissue manifest in the increased non-calcified areas in the joint slits, (e) periosteal deposits, etc., and (3) upon chemical studies of intermediary metabolism, which reveal a hypophosphatemia with normal calcium content (unless there be also tetany when there is also hypocalcemia), that is to say, a disturbance of the distribution of the calcium and phosphorus in the serum so that the calcium-phosphorus quotient is altered.

A very great step forward in our knowledge of rickets was made in 1919 when Mellanby produced rickets experimentally in dogs by means of a deficient diet. A still more important step was made in 1921 when McCollom and his associates (and Sherman and Pappenheimer, practically simultaneously) produced rickets experimentally in young rats. This experimental production of the disease in animals made easily available large numbers of test-objects upon which studies of etiology, of pathogenesis, and of therapy could be undertaken. McCollom soon showed that what had been regarded as a single vitamin called vitamin A consisted in reality of two vitamins now known as A and D, respectively, the former being important in preventing xerophthalmia and for increasing resistance to infections, the latter being the factor in food that protects against the development of rickets. These and other experimental investigators quickly devised diets (consisting usually of wheat, corn, salt and calcium carbonate) that would, with certainty, produce rickets in rats within about four weeks, the disease becoming recognizable in the animals by means of roentgenograms, as well as by studies of the blood chemistry that revealed the diminution of inorganic phosphorus.

Gradually the idea emerged that there may be more than one kind of "rickets" and, as early as 1922, Shipley and Park published an article in which they asked the question, "Is there more than one kind of rickets?" Their clinical studies concerning the association of rickets with other diseases or pathological conditions and certain peculiar manifestations of rickets, itself, in some children, had suggested the possibility that more than one kind of disturbance of mineral metabolism of the body becoming manifest in defective growth and calcification of the bones may have been included under

the head of "rickets." They then made experiments on animals and showed that when the rat is deprived of certain active light rays and a certain factor in cod-liver oil, a pathological condition like rickets in human beings can be produced through diet in either one of two ways, (1) by diminishing the phosphorus and supplying plenty of calcium or, (2) by reducing the calcium and keeping the phosphorus at a high concentration. They came to believe that these two kinds of rickets exist in human beings and that one may be called a "low-phosphorus rickets" and the other a "low-calcium rickets"; in the latter, tetany is common. They suggested, too, that the etiology of rickets may be as varied as the etiology of tetany. They even went further and postulated a special kind of rickets known as renal rickets and another kind associated with alimentary anemia. Such a development should not surprise us, for clinical medicine makes progress by resolving conditions that are at first supposed to be unitary into a series of components. I need only recall to your minds how obesity, which formerly was supposed to be one thing, has been subdivided into a whole group of obesities of differing etiology.

In this connection, one cannot help but be interested in the experiments conducted in Carlson's laboratory in Chicago. Kunde and Carlson observed rachitis-like disturbances in extreme hypothyroidism produced by thyroidectomy in animals and Kunde and Williams published a paper upon the influence of thyroid gland on the production and control of experimental rickets. They showed that cretinous rabbits (thyroidectomized between two and three weeks after birth) develop a disturbance in skeletal development that simulates rickets clinically. This disturbance, they assert, is not due to a dietary deficiency and it is accompanied by severe anemia. The blood calcium was within normal limits, but the acid soluble phosphorus of the serum was low. It was further found that no amount of cod-liver oil added to a ricket-producing diet is adequate to prevent the development of rickets in cretinous rats as determined by histological studies of the epiphyses. Moreover, in the cretinous rats, food stuffs rich in antirachitic vitamins added to a nutritious diet consisting of table scraps, did not prevent the occurrence of rickets.

These studies from Professor Carlson's laboratory seem to me

very interesting in connection with the case I have shown you today. Here we have a patient suffering from spontaneous sporadic cretinism (a high grade of hypothyroidism), and the patient has developed bony changes that have been thought by the roentgenologist to be due to rickets. Moreover, despite a daily intake of from one to three teaspoonfuls of cod-liver oil during the past year (in addition to thyroid extract), the "rickety" condition has not greatly improved, though the symptoms and signs of hypothyroidism have been much ameliorated. One wonders whether or not the form of rickets observable in this patient could correspond to the special form of experimental rickets observed by Carlson and his associates in thyroidectomized animals. One wonders still further whether alterations of the functions of the parathyroid glands could play a part in the etiology of this particular form of rickets.

On looking over the older literature of infantile myxedema, one finds that many authors had observed curvatures of the bones, swellings of the epiphyses at the wrists and at the ankles, micromelia, distended abdomen, delayed closure of the fontanelles, and delayed dentition, so that many came to believe that there was not a single case of myxedema of the child in which rachitis did not exist at the same time. Siegert, however, as early as 1900, maintained that rickets never coëxists with infantile myxedema! In a later article (1925), Siegert still asserts that congenital athyreosis with myxedema and rachitis are mutually exclusive. He makes the statement that he will not accept the diagnosis of rickets in association with infantile myxedema unless the findings in roentgenograms of the wrist-, ankle- or knee-joints give unmistakable evidences of rickets, or unless microscopic preparations revealing rickets are demonstrated to him! In view of this strong polemic, it behooves us to be very careful in making a decision as to the nature of the bony lesions resembling rickets in our little patient, as well as to the nature of the bony lesions observed in the experiments in Chicago in thyroidectomized animals.

Treatment of Rickets by Direct Radiation.—Another landmark in the development of our knowledge of rickets was the discovery of a successful treatment of rickets by direct radiation (short light waves in the ultraviolet). There was much scepticism in 1919 when Huldschinsky reported that he could thus cure the disturbances of

ossification and restore a normal blood chemistry in patients suffering from rickets, though he admitted that he could not cure the anemia of rickets by such direct radiation.

It had long been known that rickets rarely, if ever, occurs in the tropics, or in the polar regions; moreover, the good effects of air and sunlight upon rickety patients had also long been appreciated. It had further been observed that rickets is more severe during winter and spring months than during the summer.

It was soon found that the light rays that exert the maximal effect lie around 280μ , the range of efficiency lying between 313μ and 253μ . Natural sunlight yields rays between 302 and 297; thus, the most effective rays (around 280) are not present in ordinary sunlight. The quartz mercury lamp, on the other hand, yields rays down as far as 230μ . Moreover, the efficient rays in sunlight are interfered with by smoke, by fog, and by ordinary window glass, though glass that transmits the ultra-violet rays is now obtainable.

Experiments were next undertaken to discover the degree of radiation that will suffice to cure rickets in those suffering from the disease, and that will prevent it in those that are susceptible. Gradually the necessary exposure time was worked out, and it was finally found that one exposure per week, front and back—an exposure just short of that necessary for the production of erythema—will suffice.

Treatment of Rickets by Indirect Radiation.—As early as 1922, it had been suggested, in Vienna, that the effect of direct radiation might depend upon a photosynthetic formation of an antirachitic vitamin within the radiated organism. In June, 1924, Hess in New York, and in September, 1924, Steenbock in Wisconsin, almost simultaneously and apparently independently, proved that a whole series of inert food substances can be made to acquire protective properties against rickets by radiation with the quartz mercury lamp. McCollum had earlier shown that the beneficial influence of cod-liver oil in rickets is due to its content in vitamin D.

Some very strange experimental results had been reported a year or two earlier by English observers (Hume, *et al*) who stated that rats kept on a diet that produces rickets were cured by ultra-violet light, not only of their ossification disturbances, but also of

inhibited growth, but the interesting part of their report was that growth was favored even when the rats themselves were not radiated but only their cages, the rats being put back into the cages after the radiation. It turned out that this held good only when sawdust was in the bottom of the cage. Cages free from sawdust did not yield when radiated the same effects. It was shown later that the antirachitic effect was due to the fact that the rats ate the radiated sawdust! Subsequently, a very interesting experiment was made by Nelson and Steenbock (1925) upon the antirachitic action of irradiated animals upon the non-radiated when placed in the same cage. Animals that were kept on a rickets-producing diet were placed in double cages, so arranged that the upper part of the cage was separated from the lower part by a perforated floor, a layer of air 1.5 centimeter deep and the perforated roof of the lower part of the cage. If irradiated rats were placed in the upper part of the cage, then the rats in the lower part, though not irradiated, did not develop rickets; on the other hand, if the irradiated rats were placed in the lower part of the cage and the non-irradiated rats in the upper part, the latter did become rachitic—an indication that ingestion of the masses of excrement of irradiated animals, falling by gravity through the sieve separating the upper from the lower cage, exerted the antirachitic effect upon the non-irradiated animals.

After these facts concerning the possibility of "induced" or "indirect" radiation had been accumulated, it was not surprising that the idea arose that the therapeutic effect of direct radiation might depend in reality upon the antirachitic activation of some substance in the skins of the animals treated. This led to the radiation *in vitro* of calves' skin, of skin from human cadavers, and of rat's skin, and it was found that these exerted a definitely antirachitic effect, whereas non-irradiated skin fed to controls did not prevent the development of severe rickets.

Next came the study of the activation of cholesterol and of phytosterin—studies that led very quickly to still further enrichment of the doctrine of induced radiant energy. Cholesterol could be activated if exposed for a certain time to the ultraviolet rays, though, if it were exposed too long, the antirachitic power was weakened

or even destroyed, unless air was excluded during the radiation. Through spectroscopic studies, it was found that the protective substance formed on exposure of cholesterin to ultraviolet light did not come from the cholesterin itself but from a minute amount of substance apparently of sterin character that was associated with it; this was designated "provitamin." When this impurity was removed from the cholesterin, the purified substance could no longer be activated by ultraviolet light. Very soon after this, Windaus, working with another sterin, namely, ergosterin (which is present in ergot of rye and in certain yeasts), found that, on irradiation, he could obtain a substance of much stronger antirachitic activity than could be derived from radiated cholesterin. Indeed, it was 4000 times as strong! This made it probable that ergosterin was the contamination of the cholesterin, which he had earlier designated "provitamin." The researches of Windaus and Hess (1926-1927) and of Rosenheim and Webster (1926) upon this metamorphosis of ergosterol have been epoch-making. It was soon proven that the waves of ultraviolet light that activate ergosterin (so as to make it antirachitic) lie in the neighborhood of $280\text{ }\mu$. Ergosterol is present in the human skin and in the skin of animals, and it now seems certain that the effect of ultraviolet light upon the skin of man and animals is to activate this ergosterol so as to make it protective against rickets and to yield the same effects as will the administration of vitamin D. Through the discovery of this very powerful antirachitic substance, irradiated ergosterol, by means of which rickets in man and animals can not only be cured but also prevented, the earlier experiments at mass prevention by irradiated milk or milk powder, have lost much of their interest.

Excessive Dosage of Irradiated Ergosterol with Resulting Hyper-vitaminosis.—In 1927, a further fact of great importance concerning the effect of irradiated ergosterin was discovered by Pfannenstiel, who had had young rabbits under this treatment. He found that some of them lost weight, developed a cachexia, and died. On studying such animals more closely, he found that the first symptom was loss of appetite and that this was followed by emaciation, by alteration of the fur, and, sometimes, by diarrhea. If the activated ergosterol administration were stopped, the symptoms would clear

up quickly, only to reappear again when sufficient doses of the substance were fed.

Similar experiments were conducted by Kreitmair and his associates upon mice, rats, guinea pigs, and other animals. They corroborated the findings of Pfannenstiel, but they made the further observation that, after death, such animals exhibit sclerotic changes in the organs, with large lime-deposits in the arteries, kidneys, and liver. Though small doses of irradiated ergosterin will cause lime deposits in the bones in rickets, larger doses will mobilize calcium out of the skeleton and lead to its deposit in the internal organs. Fortunately, the toxic dose was found to be very far above the therapeutic and prophylactic dose of the substance.

The doses of irradiated ergosterol given to children for prophylactic purposes were soon found, in some instances, to produce marked hypercalcemia. Ordinarily, this gave rise to no symptoms, but, in some cases, symptoms appeared like those that accompany the hypercalcemia from injection of Collip's parathormone, which in sufficient doses causes anorexia, pallor, vomiting, and loss of weight.

These findings made it exceedingly important to establish the limits of safety for the administration of irradiated ergosterol, and it has since been shown that from 5 to 10 milligrams of the substance can be safely used daily as a therapeutic agent in adults, since 100 milligrams are required in them to produce sclerosis of the organs and calcinosis. In infants, 1 milligram daily was found to be a safe dose and even from 2 to 3 milligrams could be given with reasonable safety in severe cases of rickets, since it required from 5 to 10 milligrams to produce the symptoms of hypervitaminosis.

Irradiated ergosterol has been placed upon the market in the form of various preparations, usually in solution in oil. It was soon discovered, however, that different preparations of irradiated ergosterol varied in strength, owing to the fact that, on activation of the substance by ultraviolet radiation, a mixture of several active products is formed. It is even probable that the antirachitic agent formed differs from the toxic agent that causes organ sclerosis and hypercalcemia (Windaus).

The necessity of careful standardization of these preparations was obvious, and the American Medical Association has now set up standards for the preparation known as viosterol. One can obtain a viosterol that has 100 times the strength and also a viosterol that has 250 times of high-grade cod-liver oil as an antirachitic agent. Twenty drops of viosterol in oil (100 D) is equivalent to 10 teaspoonfuls of high-grade cod-liver oil in vitamin D potency. One drop of viosterol in oil (250 D) is equivalent to 1½ teaspoonfuls of standard cod-liver oil in vitamin D potency. Of course, it should not be forgotten that cod-liver oil contains vitamin A in addition to vitamin D.

For prophylactic purposes, A. F. Hess and his associates advise us to give to young infants, about 30 drops daily of viosterol (100 D), or corresponding amounts of the contained irradiated ergosterol in the preparations of greater strength. The preventive treatment of rickets thus made available ought to save mankind from now on from a plague that has been responsible through the centuries for the production of millions of cripples and for the actual spoiling of many young lives otherwise promising.

Since cod-liver oil contains this substance which we now believe to be identical with vitamin D (in addition to vitamin A), it is obviously important that cod-liver oil preparations should be carefully standardized for their content in D, since different preparations on the market have been found to vary markedly in this respect. Progress will probably be made (1) by finding the optimal method of irradiation of ergosterol so as to produce a product of constant antirachitic potency and free from toxic by-products, (2) by standardization of irradiated ergosterol, of viosterols, and of cod-liver oils by computing the potency in terms of protective or curative "rat units."

This child should continue to take thyroid extract in small doses and should also, I think, take daily 30 drops of viosterol (100 D), or 12 drops of viosterol (250 D). We cannot be sure, however, that the viosterol will have as favorable effect upon the rachitic-like bony changes in this child as we would expect in ordinary rickets, for this rickets associated with infantile hypothyroidism may, like "renal rickets," like "diabetic rickets," and perhaps other forms of

endogenous rickets, prove to be recalcitrant to the action of "bottled light."

In addition, the anemia should be combated by diet and perhaps by the administration of iron and ammonium citrate. Some *whey* may also be given, since *whey* contains most of the mineral constituents needed by the human organism and there is growing evidence that lack of certain mineral constituents may be important for the development of anemias of various sorts.

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Bio=Chemistry

RECENT ADVANCES IN CALCIUM METABOLISM

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SINCE the addition of the parathyroid hormone and the antirachitic factor to our experimental and therapeutic armamentarium great advances have been made in the understanding of the metabolism of calcium and its relation to certain disease states. The more recent contributions to our knowledge of this of particular clinical significance.

Vitamin D and Parathyroid Function.—The complex interplay of calcium metabolism has been emphasized by the work of Garrison¹ who demonstrated that the administration of parathyroid hormone to susceptible animals fails to produce the characteristic physiologic response, namely, hypercalcemia, in the presence of a deficiency in the antirachitic factor (vitamin D). These observations supplement those of Higgins and Sheard² that chicks grown in light from which the ultraviolet component has been removed invariably exhibited parathyroid hyperfunction, a change which is in all probability compensatory in nature and is prevented by ultraviolet irradiation or by the administration of ergosterol oil. Similarly, Hess, Weinstock and Rivkin³ report that the serum calcium of parathyroidectomized dogs could not be restored to normal by the administration of enormous doses of ergosterol.

Such observations explain the frequent therapeutic value of parathyroid hormone in infantile tetany in which the antirachitic factor (vitamin D) deficiency is of fundamental importance. It is now known that normal calcium metabolism depends upon several factors. It is known that the functional activity of either the antirachitic factor or the parathyroid hormone is conditioned by the presence of the other factor, and, in addition, upon the availability of calcium and phosphorus in the diet.

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Bio=Chemistry

RECENT ADVANCES IN CALCIUM METABOLISM

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SINCE the addition of the parathyroid hormone and the antirachitic factor to our experimental and therapeutic armamentarium great advances have been made in the understanding of the metabolism of calcium and its relation to certain disease states. Some of the more recent contributions to our knowledge of this subject are of particular clinical significance.

Vitamin D and Parathyroid Function.—The complex nature of calcium metabolism has been emphasized by the work of Morgan and Garrison¹ who demonstrated that the administration of parathyroid hormone to susceptible animals fails to produce the characteristic physiologic response, namely, hypercalcemia, in the presence of a deficiency in the antirachitic factor (vitamin D). These observations supplement those of Higgins and Sheard² who found that chicks grown in light from which the ultraviolet component had been removed invariably exhibited parathyroid hyperplasia. This change, which is in all probability compensatory in nature, is prevented by ultraviolet irradiation or by the administration of cod-liver oil. Similarly, Hess, Weinstock and Rivkin³ reported that the serum calcium of parathyroidectomized dogs could not be raised by the administration of enormous doses of viosterol.

Such observations explain the frequent therapeutic failure of parathyroid hormone in infantile tetany in which condition vitamin D deficiency is of fundamental importance. It is now obvious that normal calcium metabolism depends upon several factors, and that the functional activity of either the antirachitic factor or the parathyroid hormone is conditioned by the presence, in adequate amount, of the other factor, and, in addition, upon an adequate supply of calcium and phosphorus in the diet.

Pregnancy and Lactation.—It has been believed for a long time that the diminution in serum calcium which occurs in the later period of pregnancy is due in large measure to increasing calcium utilization by the foetus. Goss and Schmidt,⁴ Coons and Blunt⁵ and Macy⁶ have shown that there is an actual retention of calcium by the maternal organism during this period. This may perhaps represent the establishment of a calcium reserve in anticipation of subsequent emergencies. Hunscher⁷ has demonstrated that normal lactation constitutes such an emergency, for, despite a high intake, the transition from pregnancy to lactation was marked by a change from a distinctly positive to a markedly negative calcium balance. The calcium loss persists throughout the period of lactation, the fecal calcium at times exceeding the calcium intake, large additional amounts being lost in the milk.

These observations suggest the advisability of administering calcium salts in the later months of pregnancy and during lactation, supplemented perhaps in the latter period by vitamin D in moderate doses. Macy⁶ found that such therapy resulted in more efficient utilization of calcium by lactating women.

Hepatic Insufficiency and Eclampsia.—During the past few years Minot and Cutler,⁸ investigating the phenomena associated with carbon tetrachloride poisoning, have demonstrated in a striking manner the prophylactic and curative effects of calcium medication in that condition. They showed that the intoxication produced by carbon tetrachloride, chloroform and similar substances is perhaps due to an increased concentration of guanidine in the blood, resulting from the severe hepatic injury caused by those agents; there is, in addition, an associated hypoglycemia of marked degree. The preliminary administration of calcium salts prevents the development of the severe manifestations of the intoxication in animals, and, if given subsequent to their appearance, results in symptomatic relief and in the restoration of the normal blood-sugar level. It was at first believed that this effect was due to some pharmacologic antagonism between guanidine and calcium. Recently Minot and Cutler⁹ expressed the belief that the effect of calcium on the hypoglycemia of acute liver damage depends upon sympathetic activity.

It has been found¹⁰ that clinical conditions associated with acute hepatic insufficiency (arsphenamine hepatitis, catarrhal jaundice,

pre-eclampsia, eclampsia) present similar blood findings. Striking relief has been obtained by the administration of calcium salts, and, in some cases, parathyroid hormone.

Cantarow, Montgomery and Bolton,¹¹ investigating the partition of calcium in eclampsia, observed a pronounced decrease in the ratio of diffusible to non-diffusible calcium in that condition. This is in sharp contrast to the increase in that ratio which appears to be a constant feature of the later months of normal pregnancy, and may be related in some way to the apparent decreased availability of calcium associated with the toxic manifestations of acute hepatic insufficiency.

It now appears that the rational management of disorders of this nature should include the institution of calcium therapy and the administration of a diet high in carbohydrate and low in protein.

Hyperparathyroidism.—The experimental demonstration of the metabolic phenomena which follow the injection of the parathyroid hormone has resulted in the recognition of a hitherto unknown clinical entity, hyperparathyroidism. The diagnosis of this condition now rests on a secure basis. It has been observed most strikingly in association with the diffuse form of osteitis fibrosa cystica. The results of operative removal of either normal, hyperplastic, adenomatous or carcinomatous parathyroid glands in a number of cases has demonstrated that hyperparathyroidism forms the etiologic basis of this extremely interesting condition. The final link in the chain of evidence supporting this belief has been furnished by the work of Jaffe, Bodansky and Blair.¹² These investigators produced the typical clinical manifestations of diffuse osteitis fibrosa cystica in animals by the prolonged administration of parathyroid hormone.

The diagnosis of hyperparathyroidism rests upon the following findings: (1) Hypercalcemia; (2) Hypophosphatemia; (3) Increased urinary excretion of calcium; and (4) of phosphorus.

Apart from the bone lesions, which dominate the clinical picture, the symptomatic and objective manifestations depend upon the increased concentration of calcium in the blood. These include muscular hypotonia, diminished electrical excitability, polyuria, anorexia, constipation, metastatic calcification in various situations and nephrolithiasis.

The establishment of this condition as a clinical entity, amenable to treatment by parathyroidectomy, constitutes a distinct advance in the fields of both medicine and surgery and is one of the most important recent contributions of experimentation to clinical medicine.

Allergic Disorders.—The beneficial effects of calcium therapy in allergic disorders and in disturbances of autonomic balance such as mucous colitis and vasomotor rhinitis has frequently been noted. Considerable controversy has centered about the question as to whether or not such conditions are associated with any fundamental disturbance of calcium balance. No direct evidence of such disturbance could be demonstrated. Cantarow,¹³ in a study of cerebrospinal fluid and blood serum calcium, found a decided increase in the ratio of diffused to non-diffused calcium in a group of cases of bronchial asthma, vasomotor rhinitis, angioneurotic edema and mucous colitis. Studies of the diffusibility of calcium in the serum, employing artificial membrane methods, fail to reveal the disturbance. It appears likely that the latter methods are inadequate, inasmuch as they leave out of consideration the highly important variable factor of capillary and cell permeability. The demonstration of an increase in the *in vivo* diffusibility of calcium in this group of conditions, characterized as they are by increased cellular permeability, may prove to be of fundamental importance in the elucidation of the physical basis for allergic phenomena.

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THE CLINICAL INTERPRETATION OF BIOCHEMICAL FINDINGS—CARBOHYDRATE METABOLISM

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DIGESTION AND ABSORPTION

INGESTED carbohydrates are converted into monosaccharides by the action of enzymes present in the salivary (ptyalin), pancreatic (amylase) and intestinal (invertase, maltase, lactase) secretions. Glucose (dextrose) is the most important of these end-products, levulose and galactose being formed in smaller amounts under ordinary circumstances in adults (from sucrose and lactose respectively). These monosaccharides are absorbed from the intestine and carried to the liver in the portal circulation. The processes of digestion and absorption occur gradually, the quantity of glucose reaching the liver being less than 1.8 grams per kilogram of body weight per hour following a carbohydrate meal.

LIVER

Upon reaching the liver it is probable that galactose and levulose are converted into glycogen. Dextrose is also formed from the "carbohydrate moiety" of certain amino acids resulting from protein digestion (alanine, glycine, prolin, arginin, cystin, aspartic acid, glutamic acid) as well as from glycerol and perhaps from fatty acids.

I. *Changes in Dextrose Occurring in the Liver*

A. Storage as Glycogen (Glycogenesis)

Through the agency of specific enzymes, glucose is converted into glycogen by a process of polymerization and is stored, as such, in the glandular cells of the liver. The liver is capable of storing 150-200 grams of glycogen; this constitutes a most important carbohydrate reserve which appears to be normally the sole source of the sugar present in the blood-stream. The internal secretion of the pancreas (insulin) may play an important part in the process of glycogenesis in the liver.

B. Utilization in the Liver (Glycolysis)

A relatively small proportion of the glucose may be utilized directly in the course of the metabolic activity of the hepatic glandular cells. The process (glycolysis) appears to be one of transformation to lactic acid, with oxidation to carbon dioxide and water.

C. Passage into Systemic Circulation

The excess glucose, *i.e.*, that which cannot be stored as glycogen or utilized directly by the liver, passes into the general circulation and is carried to the tissues where it is transformed into glycogen and stored as such in the muscles or utilized for energy (glycogenolysis and glycolysis).

II. Changes in Hepatic Glycogen (Glycogenolysis)

The glycogen stored in the liver serves as a source of supply of glucose for the maintenance of the concentration of sugar in the blood and the glucose requirement of the tissues. The transformation of glycogen into glucose (termed glycogenolysis) is effected through the medium of enzyme activity (glycogenases) stimulated by one or more of the following external agencies.

A. Fall in Blood-Sugar Level

Any tendency toward a decrease in the blood-sugar concentration such as is associated with an increase in the utilization of glucose by the tissues (exercise, insulin administration) is followed by increased hepatic glycogenolysis. This phenomenon may occur through the medium of the sympathetic nervous system and adrenal secretion.

B. Adrenalin

C. Thyroxin

D. Increased Acidity

An increase in the hydrogen-ion concentration accelerates glycogenolysis, increased acidity (to pH 6.5) favoring the activity of the glycogenolytic enzyme.

E. Nervous Stimulation

Stimulation of an area in the floor of the fourth ventricle ("diabetic center") results in a discharge of liver glycogen. The impulse passes down the cord, through the splanchnic nerves, to the adrenals and the liver, the glycogenolytic effect being produced by the in-

creased secretion of adrenalin and the stimulation of the sympathetic fibers passing to the liver.

F. Ether Anesthesia

G. Asphyxia (Increased Acidity)

TISSUES

The glucose, which, being absorbed from the intestine, passes through the liver unchanged, and that which is derived from hepatic glycogenolysis, pass in the arterial blood to the tissues where the following phenomena occur:

I. *Glycogenesis*

The muscles contain a store of glycogen comparable in amount to that of the liver. From this is derived, by glycogenolysis, the glucose required for the metabolic activities of the tissues. As this glycogen reserve is drawn upon, glucose is abstracted from the blood and is transformed into glycogen (tissue glycogenesis). It is apparently this phase of carbohydrate metabolism which is dependent upon the action of insulin. The glucose which results from glycogenolysis in the tissues and which is utilized in their metabolic processes differs in some way from that derived from hepatic glycogenolysis which cannot be so utilized. The latter must be converted into tissue glycogen before it can supply the energy requirements of the body. Since insulin is essential for this transformation, in its absence the circulating glucose is incapable of being utilized by the tissues. The function of hepatic glycogen is therefore the maintenance of the blood-sugar level; that of tissue glycogen is to furnish glucose for combustion in the tissues. The latter normally plays no part in the maintenance of the blood-sugar concentration. The action of pituitrin appears to be one of insulin antagonism, *i.e.*, it appears to inhibit glycogenesis in the tissues. Some believe, however, that it acts in a manner similar to thyroxin and adrenalin.

II. *Glycogenolysis*

As the nutritional and energy requirements of the tissues demand, stored glycogen is transformed into glucose. This process, as in the liver, is favored by increased acidity. Muscular contraction is associated with the conversion of glycogen into lactic acid,

20 per cent. of which is completely combusted into carbon dioxide and water, 80 per cent. being reconverted into glycogen.

POSTABSORPTIVE BLOOD SUGAR

The concentration of glucose in the blood is the resultant of forces which affect the liberation of glucose from glycogen stored in the liver and those which affect its withdrawal from the bloodstream and its deposition, as glycogen, in the tissues. It is obvious that in determining the sugar concentration of venous blood one is obtaining the amount of glucose remaining after the removal of a portion during its passage through the tissues; the sugar content of arterial (capillary) blood represents the glucose supplied to the tissues. Consequently the arterial-venous difference represents the degree of glucose utilization in the tissues.

In the postabsorptive state the concentration of glucose in arterial (capillary) blood is practically the same as in venous blood. Friedenson states, "At all times glucose is being absorbed from the blood by the muscles and other tissues to be stored as glycogen, which is, in turn, continually decomposed to lactic acid and oxidized. The rate of removal is, in the resting, fasting state, however, too small to be readily distinguished. The blood sugar is as continuously replenished from the hepatic stores of glycogen, which are obtained from ingested preformed glucose or by the transformation in the liver of other carbohydrates or proteins."

The establishment of normal limits for blood sugar is complicated by the presence, particularly in the red corpuscles, of a non-sugar copper-reducing substance which is probably largely glutathione (44-60 milligrams per 100 cubic centimeters). The determination of venous blood sugar by the Benedict 1928 reagent yields results ranging normally from 65 to 100 milligrams per 100 cubic centimeters, which appear to represent true sugar values. Normal figures obtained by other commonly used methods are: Folin-Wu, 80-120 milligrams; Folin-Wu modified, 70-110 milligrams; Shaffer-Hartmann, 85-125 milligrams; Hagedorn-Jensen, 95-135 milligrams per cent. The discrepancy depends upon the fact that the Benedict 1928 reagent, which may be used with the Folin-Wu tungstic acid filtrate, is unaffected by glutathione, whereas the reagents used in the other methods are affected by this substance. Further-

more, it is now recognized that the Folin-Wu method, which is extensively employed in this country, gives results which are too high for high sugar values and too low for low values. For instance, near the 50-milligram level the results obtained are 15-18 per cent. less than the true value. The use of the Benedict 1928 reagent obviates the possibility of errors of interpretation due to this inaccuracy of method. In order to obtain true postabsorptive values the subject must be at complete mental and physical rest. Pain, emotional excitement, apprehension, fear, anger, *etc.*, may raise the blood sugar above the resting level, probably through the medium of excessive secretion of adrenalin, resulting in increased hepatic glycogenolysis.

NORMAL ALIMENTARY REACTION (ABSORPTIVE RESPONSE). BLOOD SUGAR TOLERANCE

The ingestion of glucose, starch, and, to a certain extent, other carbohydrates (levulose) and proteins, is followed in the normal individual by an increase in the blood-sugar concentration. The degree of elevation depends to a certain extent upon the amount of carbohydrate ingested but the relationship is not exactly quantitative. Practically identical responses are elicited by the administration of glucose in amounts ranging from 50 to 150 grams. This alimentary reaction forms the basis for the commonly employed carbohydrate tolerance test, several varieties of which have been described. Perhaps the most satisfactory for routine purposes is performed as follows:

A specimen of venous blood is collected from the patient after a fast of at least twelve hours. Administer 1.75 grams of glucose per kilogram of body weight in 40-50 per cent. solution, flavored, if desired, with the juice of one lemon. Specimens of blood are collected at twenty- to thirty-minute intervals over a period of two hours or more. If the curve of arterial blood sugar is desired specimens of capillary blood are obtained from the finger or lobe of the ear at the same time as those from the vein. The concentration of sugar is determined in each specimen, the micro method being used for capillary blood. It is also desirable to have the bladder emptied before administering the glucose and to collect additional urine specimens after two hours and over the remainder of the

twenty-four-hour period for the purpose of determining their glucose content.

The test may be simplified by administering an arbitrary amount of glucose (50-100 grams) and by diminishing the number of blood specimens. A fasting specimen should always be taken if possible. Samples may then be withdrawn hourly or a single specimen may be taken at the end of two to three hours, at which time the blood sugar will normally have returned to its resting level.

The characteristics of the normal venous blood-sugar curve are as follows:

(a) The blood sugar rises sharply to reach a maximum of 140-160 milligrams per 100 cubic centimeters (Folin-Wu) within the first hour (usually forty to forty-five minutes).

(b) A return to at least 120 milligrams at the end of one and one-half to two hours and to the postabsorptive level or below in two and one-half to three hours.

The characteristics of the normal arterial (capillary) blood sugar curve are as follows:

(a) A more rapid and more pronounced rise than that of venous blood sugar. At the peak (forty to forty-five minutes) the arterial blood sugar is from 10-50 milligrams higher than the venous blood sugar (arterial-venous differences), the average difference being about 25 milligrams per 100 cubic centimeters.

(b) The return to a normal level is not so rapid as in the case of venous blood sugar, the two curves converging at the resting level or below in two and one-half to three hours.

Glucose should not be present in abnormal quantity in any specimen of urine.

The factors which determine the normal alimentary reaction should receive brief consideration.

I. Rise of Blood Sugar

The initial rise in both arterial and venous blood sugar is due in large measure directly to the glucose absorbed from the intestine. Some believe, however, that an important part is played by the liberation of glucose from hepatic glycogen (hepatic glycogenolysis) induced by an increase in the hydrogen-ion concentration in the liver (outpouring of alkaline pancreatic and intestinal secretions).

II. Arterial-venous Difference

This is an expression of the rate of removal of glucose from arterial blood by the tissues, particularly the muscles, for the formation of glycogen and eventual conversion into lactic acid or combustion. This process (tissue glycogenesis) is dependent chiefly upon the action of insulin.

III. Fall in Blood Sugar

This appears to be due largely to two factors:

- A. The removal of sugar by the liver to form glycogen.
- B. The removal of sugar by the tissues to form glycogen.

It is believed that the hyperglycemia caused by the administration of glucose stimulates the glycogenetic mechanism, the resulting increased glycogenesis causing the fall in blood sugar following the primary rise. Once initiated, this process continues to operate until the blood-sugar concentration has fallen below the postabsorptive level (three to four hours), thus producing the normal period of postalimentary hypoglycemia.

A third factor appears to be operative and is undoubtedly of importance.

- C. Distribution of water between the intestine and the blood.

Woodyatt, referring to the experimental work of Fisher and Wishart says, "There was no increase of the blood volume during the first hour, the hemoglobin percentage remaining unchanged, probably because the large quantity of glucose in the bowel held water there. But in the second hour the blood volume became large and the hemoglobin showed the effects of dilution. In this same hour the sugar percentage returned to normal. But the absorption of glucose was only completed in the fourth hour and calorimetric observations by Lusk showed that the metabolism also ran at a uniform rate 20 per cent. above the basal level into the fourth hour. Accordingly the observed sugar percentages first rose as the rate of sugar supply was increased, but fell again during the maintenance of this increased supply and while the metabolism was constant, owing to the shifting of water."

The state of carbohydrate nutrition has a definite influence upon the alimentary glucose response of normal individuals. An adequate deposit of glycogen in the liver and other tissues is essential to the

production of a normal response as above described. If the subject is in a state of relative carbohydrate starvation the rise in blood sugar following the ingestion of glucose will be more pronounced and its fall more delayed than under normal conditions; this is thought to be due to the existence, under such circumstances, of a relatively high threshold of sensitivity to stimulation of the glycogen-forming mechanism. Conversely, if the organism is in a state of carbohydrate saturation, *i.e.*, if a high carbohydrate meal has been taken within two to three hours of the performance of the test, the rise in blood sugar will be distinctly less marked than that described above. This phenomenon is probably due to the fact that the activity of the mechanism of glycogenesis, initiated by the previous meal, has not yet subsided and that the active removal of glucose from the blood, still well under way, prevents the marked rise in blood sugar which would otherwise have followed the ingestion of glucose.

It is, therefore, important that the subject shall have partaken of a well-balanced meal on the evening prior to the performance of the test. The ingestion of a meal high in fat and low in carbohydrate may result in a curve typical of a state of carbohydrate starvation.

EFFECT OF OTHER SUGARS

I. *Levulose (Fructose) Tolerance*

The metabolism of levulose differs from that of glucose in that it appears to be incapable of transformation into glycogen except by the liver. The difference between the behavior of these two sugars may be illustrated by certain experimental observations.

(a) In the absence of insulin (depancreatized dogs) levulose will be stored as glycogen in the liver; glucose will not.

(b) Insulin hypoglycemia is relieved by glucose much more effectively than by levulose.

(c) Following the ingestion of levulose there is comparatively little rise in blood sugar and practically no arterial-venous difference, indicating the minor rôle of the muscles in removing this sugar from the blood.

(d) Cori has found that although levulose is absorbed from the intestine much more slowly than glucose, at the end of four hours the amount of glycogen formed in the liver by the former was 39 per cent. and by the latter, 17 per cent. In the absence of hepatic

disease or functional insufficiency the ingestion of levulose, in tolerance doses, is followed by comparatively little elevation of blood sugar, since, after absorption, it is effectively removed from circulation by the liver where it is stored as glycogen. The levulose-tolerance test has therefore been utilized as a test of the integrity of liver function.

It is performed as follows (Tallerman):

A sample of blood is taken in the fasting state. Forty-five grams of levulose (glucose-free) are ingested, dissolved in 200 cubic centimeters of water or lemonade. Samples of blood are withdrawn at half-hour intervals over a period of two hours and the sugar content of all specimens determined. A normal response is characterized by:

(a) A maximum rise of less than 30 milligrams per 100 cubic centimeters above the postabsorptive level.

(b) A return to the resting level in one and one-half hours.

II. *Galactose Tolerance*

Galactose, like levulose, is removed from the blood chiefly by the liver, although, according to Rowe, the glands of internal secretion have an important influence upon the tolerance of the organism for this sugar, as for glucose. There is considerable variance of opinion regarding the effect of the ingestion of galactose upon the blood-sugar concentration. Some investigators report a more pronounced reaction than that obtained with glucose. In such cases, however, the quantity of galactose administered has been excessive (100 gm.). It has been found that the normal limit of tolerance for this sugar is approximately 40 gm. in females and 30 gm. in males. If 40 gm. are administered to normal subjects there is little or no alteration in the blood-sugar level; hyperglycemia occurs rarely if at all, even with doses of 60 gm., and the arterial-venous difference observed after glucose ingestion is absent.

PHENOMENA ASSOCIATED WITH NORMAL ALIMENTARY GLUCOSE REACTION

From the laboratory standpoint, there are two significant phenomena associated with the normal alimentary glucose reaction; both are indicative of increased glucose utilization.

I. Decreased Serum Phosphate Concentration

The inorganic phosphate of the blood appears to be intimately related to the intermediary metabolism of glucose. It is probable that the formation of a hexose-phosphate compound is an essential step in the process of utilization of glucose in the tissues. Consequently, during this process, inorganic phosphate is withdrawn from the blood, the phosphate content of the tissues, particularly muscle, being correspondingly increased and its excretion depressed. These changes in phosphate occur independently of the level of blood sugar; when increased carbohydrate utilization is induced by the administration of insulin the same phenomena are observed as when glucose is administered to a normal individual, although in the former instance the blood sugar is reduced and in the latter case it is elevated. It is obvious that the determination of blood phosphate during the performance of the glucose-tolerance test may be of distinct clinical value in cases in which the interpretation of the blood-sugar curve is difficult. The hypophosphatemia which normally occurs has the same theoretical significance as the arterial-venous difference, *i.e.*, integrity of pancreatic islet function and normal tissue utilization of glucose.

Following the oral administration of 100 gm. of glucose or of 1.75 gm. per kilogram of body weight, as in the Janney test, the serum inorganic phosphate concentration falls 1-1.5 milligrams per 100 cubic centimeters, reaching a minimum in about one and one-fourth to one and one-half hours, then gradually rising to attain the resting level in four to five hours. This period (of from four to five hours) represents the period of what may be called active carbohydrate utilization.

In the presence of a normal storage mechanism (insulin) this curve is produced by any agency which increases the supply of glucose to the tissues and hence by factors which stimulate hepatic glycogenolysis. These include epinephrin, thyroxin, and ether anesthesia. Pituitrin, which gives rise to hyperglycemia, apparently not through increasing hepatic glycogenolysis but by inhibiting insulin activity and so depressing tissue glycogenesis, causes either no alteration in serum phosphate or, in many instances, a slight increase.

II. Increased Respiratory Quotient

An increase in the respiratory quotient above the normal resting level (0.82) is one of the most exact indications of carbohydrate utilization (storage and combustion). If respiratory quotient determinations are carried out simultaneously with the blood-sugar tolerance test it is found that in the normal subject no significant change occurs until after the blood sugar begins to drop. At the end of one to one and one-half hours the respiratory quotient rises from 0.82 to 0.88-0.90, reaching 0.95 or 0.96 in about two hours and then gradually decreasing to reach the resting level in about four hours. This period, coinciding with that of hypophosphatemia, represents the period of increased carbohydrate utilization. The respiratory quotient is likewise influenced by the factors enumerated in the consideration of the relation of serum phosphate to carbohydrate metabolism.

ABNORMALITIES OF POSTABSORPTIVE BLOOD-SUGAR LEVEL

I. Fasting Hyperglycemia

From what has been said previously it is evident that an increase in the fasting blood-sugar level may be due to one or both of two mechanisms: (a) an increased rate of hepatic glycogenolysis, causing the passage of glucose into the blood-stream at a rate too rapid to allow of the complete removal of the excess by the tissues; (b) a decrease in the capacity of the tissues for removing glucose from the blood (decreased tissue utilization).

A. Increased Hepatic Glycogenolysis

The clinical importance of this factor is not sufficiently appreciated. It should be recognized that fasting hyperglycemia, although highly suggestive, is not synonymous with diabetes mellitus and that the utmost care must be exercised to exclude all other causes of hyperglycemia before arriving at that diagnosis.

1. Hyperthyroidism: Hyperthyroidism, whether due to thyroid disease (exophthalmic goiter, toxic adenoma) or temporarily induced by the administration of thyroid gland substance or thyroxin, results in a state of hypersensitivity on the part of the liver for the conversion of glycogen into glucose. This glycogenolytic action

of thyroxin may be excited directly, but it is more probable that the effect is produced by rendering the liver hypersensitive to sympathetic nerve impulses, and possibly to adrenalin, since section of the splanchnic nerves prevents the discharge of glycogen.

In the presence of an adequate supply of glycogen in the liver there is a distinct tendency toward a state of fasting hyperglycemia, the tissues being constantly subjected to the necessity of handling a superabundance of glucose. This, unless excessive, is undoubtedly compensated by increased activity of the storage mechanism and increased combustion of glucose in the tissues. Obviously, unless carbohydrates are supplied in abundance, the store of hepatic glycogen will be depleted and the blood sugar will automatically fall and may become subnormal. This perhaps accounts for the relatively infrequent incidence of fasting hyperglycemia in patients with hyperthyroidism. The blood-sugar concentration is found to be above normal in 5-10 per cent. of such individuals.

The mistake should not be made of interpreting a disturbance of carbohydrate metabolism dependent upon hyperthyroidism as due to diabetes mellitus. Further details of the laboratory means of differentiating these conditions are now being investigated. The patient with hyperthyroidism is undoubtedly more prone to develop diabetes than other individuals, the combination being encountered by Joslin and Lahey in 1.44 per cent. of 4,917 true diabetics. In an additional 4.2 per cent. some degree of thyroid enlargement was present without definite evidence of hyperthyroidism.

2. Increased secretion of epinephrin: The hepatic glycogenolytic action of epinephrin has been referred to previously. If the glycogen content of the liver is adequate the injection of epinephrin is followed by a rise in blood sugar. This fact has been utilized as a test of the glycogen storing capacity of the liver. If 10 minims of a 1:1000 solution of epinephrin hydrochloride are injected intramuscularly, the blood sugar rises 35-45 milligrams per 100 cubic centimeters in three-fourths to one hour and returns to the resting level in one and three-fourths to two hours.

This effect of epinephrin is probably involved in many physiologic processes.

a. As indicated above it appears to be an essential factor in
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the production of the hyperglycemic response to increased thyroid activity.

b. Cannon believes that hypoglycemia, produced characteristically by the administration of insulin, results in increased sympathetic activity and increased adrenal secretion with consequent mobilization of sugar from the liver. As Lusk states, this "arrangement represents another remarkable example of automatic adjustment when a disturbance threatens the equilibrium of the organism."

c. Cannon and his associates have shown that various emotional states, such as anger and fear, are associated with an increased quantity of epinephrin in the blood. These states as well as conditions of mental stress, excitement and excessive cold have been found to be accompanied by an increase in blood sugar, apparently the result of the mobilization of liver glycogen by epinephrin. Pain perhaps acts in a similar manner. These conditions constitute what may be termed psychic hyperglycemia.

d. Increased adrenal secretion is a factor in the production of hyperglycemia in the so-called diabetic picture and in intracranial disorders (concussion, brain tumor and fracture of the skull with increased intracranial pressure) which cause the transmission of impulses through the splanchnic nerves to the adrenals and liver.

The hyperglycemia which follows the administration of epinephrin is accompanied in the normal individual by a decrease in the inorganic phosphate content of the blood serum and an increase in the respiratory quotient, phenomena indicative of an increased supply of glucose to the tissues and an increase in glucose utilization; the latter process is not directly influenced by epinephrin.

3. Increased hydrogen-ion concentration: The optimum hydrogen-ion concentration for the activity of the glycogenolytic enzyme (glycogenase) is about pH 6.5. Since the normal hydrogen-ion concentration of the blood is about pH 7.32 it is evident that increased acidity will favor hepatic glycogenolysis and will so tend to produce hyperglycemia.

a. Ketosis in diabetes mellitus: This factor is of particular importance in diabetes mellitus because it aggravates a preexisting hyperglycemic mechanism, in this case hypoinsulinism. In the evaluation of the significance of the fasting blood-sugar concentra-

tion in this disorder it is important to attempt to determine what proportion of the elevation is dependent upon the complicating state of acidosis (ketosis). It is because of the hyperglycemic tendency in acidosis that such patients are relatively resistant to insulin; the recognition of this fact is therefore of great importance from the standpoint of therapy.

b. Ether and chloroform anesthesia: The exact cause of the acidosis of ether and chloroform anesthesia is not known but it is well established that the hydrogen-ion concentration of the blood increases rather suddenly during the induction of anesthesia and then rises gradually during its maintenance. Although the ether and chloroform may exert a direct glycogenolytic influence upon liver glycogen, it seems more likely that the acidosis plays a major rôle in the production of this effect. A remarkable rise in blood sugar may occur during anesthesia. The degree of hyperglycemia is dependent upon the amount of glycogen in the liver, the quantity of anesthetic administered and upon the adequacy of the mechanism of carbohydrate utilization.

In the absence of any other factor which tends to produce hyperglycemia, such as hyperthyroidism and diabetes mellitus, the blood sugar has been found to rise 7-8 milligrams per 100 cubic centimeters per ounce of ether administered. These figures may be greatly increased, if the anesthetic is not skilfully administered, by the introduction of complicating factors such as excessive muscular effort, excitement and asphyxia. In diabetes mellitus the degree of hyperglycemia is much more marked as the excessive amount of glucose entering the blood-stream cannot be adequately utilized by the tissues. The duration of anesthesia hyperglycemia, usually four to twelve hours after operation, depends upon the quantity of anesthetic used and the duration of the state of anesthesia. The rise appears to be more pronounced in laparotomies than in extra-abdominal operations but it is otherwise independent of the nature or severity of the operative procedure. Values as high as 400 milligrams per 100 cubic centimeters have been observed in individuals with normal carbohydrate metabolism.

If the quantity of glycogen stored in the liver is deficient, as in hepatic insufficiency (jaundice), the blood sugar cannot rise as in normal individuals and there is great danger of depletion of the

hepatic glycogen reserve with consequent serious damage to the liver by the ether or chloroform which have a profound toxic effect upon the liver parenchyma.

c. Asphyxia: Asphyxia, whether mechanical or occurring during anesthesia, particularly with nitrous oxide and ethylene, is accompanied by an increase in blood sugar. The two anesthetic agents mentioned do not, in the absence of asphyxia, have any appreciable effect upon the blood-sugar concentration. Asphyxia produces this effect through the medium of the associated increase in hydrogen-ion concentration which increases the mobilization of hepatic glycogen. The blood sugar may rise 20-40 milligrams per 100 cubic centimeters after the administration of morphine, the mechanism probably being similar to that involved in asphyxia.

d. Acidosis due to other causes, as fever, nephritis and dehydration, may result in an increase in the level of blood sugar. The rise in such cases is not marked, but, occurring in association with other factors, their influence may be significant.

4. Convulsions or strenuous muscular exercise cause a liberation of glucose from the liver with resulting hyperglycemia. This has been mentioned previously in connection with the discussion of the influence of epinephrin. An increased fasting blood sugar may therefore be found in such conditions as eclampsia, essential epilepsy, uremic convulsions, Jacksonian epilepsy, tetany, tetanus, etc. It must be realized that, as in all conditions acting through the agency of increased hepatic glycogenolysis, hyperglycemia can be produced only if the reserve supply of liver glycogen is abundant. When this is depleted, if the glycogenolytic agent continues to operate and carbohydrate is not supplied, the blood-sugar concentration decreases and, eventually, hypoglycemia results. This fact is perhaps responsible for the contradictory reports of the blood-sugar level in eclampsia and other convulsive states. Similarly, strenuous muscular exertion, in a normal individual, is at first associated with an increase and later, if continued, with a decrease in blood sugar, the source of supply having been virtually exhausted.

B. Decreased Tissue Utilization (Tissue Glycogenesis)

Hyperglycemia dependent upon this condition is due to a decrease in the capacity of the tissues for removing glucose from the blood so that, although the rate of its discharge from the liver may

be normal or, indeed, subnormal, it exists in the blood in increased concentration in the fasting state.

1. Hypoinsulinism (diabetes mellitus): The fundamental fault in diabetes mellitus is a deficiency in pancreatic islet secretion (insulin). The exact way in which insulin acts in the intermediary metabolism of carbohydrates is not definitely understood but it appears to be essential for the polymerization of glucose into glycogen in the tissues and, perhaps, the liver. Since this process (tissue glycogenesis) is a necessary preliminary to the utilization of glucose in the tissues, the latter cannot proceed at a normal rate if the supply of insulin is deficient. The obvious consequence is an increase in the concentration of glucose in the blood.

In large series of cases of diabetes mellitus the postabsorptive blood sugar has ranged from 70 to 1700 milligrams per 100 cubic centimeters of blood. Complicating conditions such as acidosis, which should be considered a part of the disease, and hyperthyroidism, naturally tend to maintain the blood sugar at a higher level than that due to the insulin deficiency *per se*. Although it is true that the level of the fasting blood sugar usually parallels the severity of the condition, such a statement cannot be made unequivocally. In early cases the fasting blood sugar may be well within normal limits; as the condition becomes more advanced values of 180-300 milligrams may be obtained; in advanced cases values of 400 milligrams are not uncommon and, if acidosis is marked and the patient in coma, the degree of hyperglycemia may be extreme (700 milligrams or over). Figures above 600 milligrams are, however, rarely observed. In interpreting figures above 200 milligrams per 100 cubic centimeters it must be recalled that the Folin-Wu method yields results which are consistently too high for high sugars and that, within the normal range, it yields results 15-20 milligrams higher than those obtained with the Benedict 1928 reagent. In view of this discrepancy the analytic method employed should always be recorded, particularly in border-line cases.

In some instances the postabsorptive blood-sugar concentration does not afford a true index of the presence or severity of an existing diabetes. As has been stated, in mild cases the fasting blood sugar may be within normal limits and further studies, such as the glucose tolerance test, must be resorted to in order to establish the true na-

ture of the condition. Fasting hyperglycemia (above 130 milligrams per 100 cubic centimeters) is highly suggestive of diabetes mellitus but other conditions previously mentioned, as well as some cases of chronic arterial hypertension, must be considered. In the presence of complicating factors, particularly hyperthyroidism, the diagnostic standard must be raised. Joslin and Lahey state, "To avoid premature diabetic cures, we have raised the standard for a diagnosis of diabetes in hyperthyroidism to a blood sugar of 150 mgm. per cent. fasting or 200 mgm. per cent. or more after meals in addition to glycosuria."

It has been definitely established that the presence of glucose in the blood is dependent upon hepatic activity. Removal of the liver in completely diabetic (depancreatized) animals results in the disappearance of sugar from the blood as in the case of non-diabetic animals. Advanced acute hepatic disease with serious disturbance of the glycogenic function of the liver, occurring in a patient with diabetes, tends to diminish the blood-sugar concentration. This condition is not frequently encountered (phosphorus or arsenic poisoning, toxemias of pregnancy, acute diffuse necrosis of liver, occasionally in acute catarrhal jaundice). A similar tendency occurs in undernourished individuals, whose carbohydrate and protein have been so restricted that the available glycogen stores in the liver have been depleted. Under these circumstances the postabsorptive blood-sugar level may mask the severity of the diabetic condition. On the other hand, as has been indicated, hyperthyroidism, hypertension, nephritis, acidosis and acute infections occurring in a patient with diabetes mellitus may, by their independent hyperglycemia effect, exaggerate the apparent severity of the condition. It should be realized, however, that the metabolic error in diabetes is seriously aggravated by factors which increase hepatic glycogenolysis, such as hyperthyroidism, infection and acidosis, and that their presence is of definitely adverse prognostic import.

2. Hyperpituitarism: Increased activity of the posterior lobe of the pituitary gland produces an effect similar to that caused by insulin deficiency. Pituitrin appears to act in a manner antagonistic to insulin; *i.e.*; it depresses glycogen formation in the tissues. Some

believe that the action of pituitrin is similar to that of epinephrin, but there is much evidence to support the former view. Patients with hyperpituitarism (acromegaly) frequently exhibit a distinct tendency toward fasting hyperglycemia, which is seldom pronounced but is usually evidenced in the form of diminished tolerance to ingested carbohydrate.

II. *Fasting Hypoglycemia*

Postabsorptive hypoglycemia is encountered much less frequently than hyperglycemia. However, with the development of more specific knowledge regarding the influence of the liver and pancreas upon carbohydrate metabolism, hypoglycemia has achieved a clinical significance which was formerly lacking. The factors which tend to lower blood sugar are the opposite of those which have been dealt with in the discussion of hyperglycemia. They may be considered under two main headings:

- A. those which decrease the rate of hepatic glycogenolysis and
- B. those which increase the rate of removal of glucose from the blood (increased tissue glycogenesis and utilization).

A. Decreased Hepatic Glycogenolysis

Since the normal blood-sugar level is maintained by glucose resulting from the mobilization of liver glycogen it naturally follows that depression of the mechanism of hepatic glycogenolysis will be associated with a hypoglycemic tendency. Clinically this occurs in two groups of conditions: (1) those in which the primary effect is exerted upon the glycogenolytic process, the amount of glycogen stored in the liver being normal, or at times, increased; (2) those in which the primary fault lies in a marked diminution in the glycogen content of the liver so that it cannot respond to the demands of the organism for glucose.

1. Primary depression of hepatic glycogenolysis

a. Hypothyroidism: In myxedema and cretinism the blood-sugar concentration may be extremely low, values of 50-60 milligrams per 100 cubic centimeters (Folin-Wu) having been reported. Values of 70-80 milligrams are commonly observed. A marked drop in blood sugar (60 milligrams per cent.) may occur at times immediately following thyroidectomy, particularly in individuals who

have not received adequate amounts of carbohydrate before operation.

b. Hypoadrenalinism: In Addison's disease, usually associated with tuberculosis of the adrenal glands, the blood sugar is frequently but not invariably found to be subnormal. The average value in a large series of collected cases was 75 milligrams per cent. In a few instances figures of 30-40 milligrams have been reported, usually in fatal cases shortly before death. Hypoglycemia occurring as a terminal event in extensive burns (0-30 milligrams) has been attributed to suprarenal failure. Longcope reported a case of scleroderma with a blood sugar of 41 milligrams per cent. in which, at autopsy, one suprarenal gland was found to be atrophied.

2. Depletion of hepatic glycogen

Since the demonstration, by Mann and Magath, of the essential part played by the liver in the maintenance of the normal blood-sugar level, several cases of hepatogenic hypoglycemia have been reported. The liver is endowed with such an extensive functional reserve capacity and with such remarkable regenerative powers that its glycogenic function is seriously impaired only in the late stages of chronic diseases such as cirrhosis. Blood-sugar values of 50-60 milligrams per cent. may be observed in the terminal stages of cirrhotic processes, particularly in obstructive biliary cirrhosis but occasionally in the portal type. Hypoglycemia may be a terminal event after operations for biliary-tract disease under general anesthesia which may exhaust a glycogen reserve already depleted by associated hepatic disease (hepatitis).

Spontaneous hypoglycemia occasionally occurs in diabetic patients and may possibly be attributed to temporary depletion of liver glycogen which is greatly decreased in amount in that condition.

It is in the acute, rapidly progressive and extensive forms of hepatic disease that hypoglycemia is most commonly observed. Values as low as 25-40 milligrams per 100 cubic centimeters have been reported in cases of phosphorus poisoning, chloroform and carbon-tetrachloride poisoning and following arsphenamine. Severe acute infections, such as diphtheria and scarlet fever, may produce similar grades of hypoglycemia, perhaps in the same manner,

although suprarenal insufficiency may be a factor in such cases. Extremely low values have been observed in acute yellow atrophy or acute diffuse necrosis of the liver (15-50 milligrams). Marked hypoglycemia (25 milligrams) has been reported in association with primary liver cell carcinoma replacing 70-80 per cent. of the liver substance; at the time of death the blood sugar had fallen to 13 milligrams per 100 cubic centimeters. It is important to realize that other disturbances of function may not be demonstrable in spite of the fact that hepatic damage may be so extensive that the glycogen content of the liver is extremely low. The consideration of the state of the glycogen reserve is of the utmost importance in surgical disorders of the biliary tract since the administration of ether in such cases, by depleting this reserve, may result in serious consequences (post-anesthetic hypoglycemia). Excessive, continued muscular exertion may be associated with hypoglycemia following the primary period of hyperglycemia, due likewise to exhaustion of hepatic glycogen; this is also true of convulsive disorders such as strychnine poisoning, eclampsia, uremia and tetanus.

B. Increased Tissue Utilization of Glucose

1. Hyperinsulinism and dysinsulinism: Since the introduction of insulin, hypoglycemia occurs much more frequently than formerly. Following its subcutaneous administration the blood-sugar concentration falls, reaching a minimum in two to six hours, the degree of reduction depending upon the amount of insulin administered. Symptoms of hypoglycemia usually occur when the blood-sugar level reaches 60-45 milligrams per 100 cubic centimeters (Folin-Wu) although some patients apparently have an extraordinary tolerance for low levels of blood sugar. In a case of diabetes reported by Peters and Rabinowitch the blood sugar ranged from 21-31 milligrams per cent. over a period of six hours without symptomatic manifestations. Since values below 25 milligrams probably represent non-glucose reducing substances by the Folin-Wu method, sugar was probably practically absent from the blood-stream in this case. It is obvious that hypoglycemia of any degree can be induced by the injection of insulin, the responsiveness of the individual varying within rather wide limits.

Apart from this form of induced hyperinsulinism, a similar mechanism may be brought into play by other means. In normal

individuals, two and one-half to three and one-half hours after the administration of carbohydrate or epinephrin there is a period of mild hypoglycemia (70-80 milligrams per cent.) following the primary rise in blood sugar. This is believed to be due to the fact that the mechanism of glycogen storage, stimulated by the rise in blood sugar, acquires a momentum which carries the process beyond the period of increased glucose supply. It occurs, under normal conditions, whenever insulin secretion is stimulated by an increased quantity of glucose reaching the tissues.

Several cases of spontaneous hypoglycemia due to hyperinsulinism or dysinsulinism of endogenous origin have been reported. In these cases the blood sugar has been found to be as low as 38-50 milligrams per cent. The pathologic lesions have been found to be pancreatic island hyperplasia and adenoma and carcinoma of the islands of Langerhans. The differentiation of such cases from those of primary hepatogenic hypoglycemia is at times difficult. In some cases the blood-sugar level is not consistently subnormal, the patient experiencing hypoglycemic crises associated with marked subjective and objective manifestations.

2. Hypopituitarism: Diminished pituitary secretion such as occurs in the late stages of acromegaly and in Frohlich's syndrome may be associated with mild hypoglycemia; the blood-sugar concentration is rarely below 70 milligrams per cent. (Folin-Wu). This diminution is believed by many to be due to a disturbance of the balance between pituitrin and insulin which are mutually antagonistic, the result being a state of relative hyperinsulinism.

Hypoglycemia of moderate grade has also been reported in cases of status thymicolymphaticus and in progressive muscular atrophy. Its cause is not clearly understood and it is seldom of sufficient degree to produce symptoms.

ABNORMAL ALIMENTARY RESPONSE

I. *Exaggerated Response—Diminished Glucose Tolerance*

By diminished glucose tolerance is meant inability of the organism to handle ingested glucose as efficiently as a normal organism; it indicates inefficiency of one or more of three factors involved in the normal intermediary metabolism of carbohydrates:

A. Inadequate glycogen storage in the liver, so that glucose

reaching the liver in the portal blood is not adequately removed, and, as a result, enters the systemic circulation in abnormal amounts. The chief clinical conditions in which this factor plays an important part are those in which there is extensive and rapidly progressive hepatic disease, such as acute or subacute necrosis (yellow atrophy), arsphenamine hepatitis, phosphorus, chloroform and carbon-tetrachloride poisoning, acute alcoholism, acute toxic hepatitis, hepatitis associated with biliary-tract disease, obstructive jaundice and acute catarrhal jaundice.

B. Increased hepatic glycogenolysis. In this group are included hyperthyroidism, hyperadrenalinism, acidosis and toxemia due to acute infections, such as lobar pneumonia, diphtheria, scarlet fever, etc.

C. Decreased tissue utilization. If the ability of the tissues to form glycogen from circulating glucose is diminished, an excess remains in the blood. The most important clinical condition in this group is diabetes mellitus (hypoinsulinism); hyperpituitarism probably belongs under this heading.

The chief features of the blood-sugar curve following the ingestion of glucose which characterize a diminished glucose tolerance are:

- (a) An abnormally high rise in the venous blood-sugar concentration (above 160 milligrams per cent.).
- (b) The maximum concentration is reached later than in the normal individual (after one hour).
- (c) The period of hyperglycemia is protracted more than normal.
- (d) The return to the postabsorptive level is delayed (more than two hours).
- (e) Increase or decrease in the arterial-venous difference may be associated with one or more of these phenomena.

A. Inadequate Hepatic Glycogenesis

As stated by Friedenson, "If the sugar which enters the blood after the ingestion of glucose is removed both by the tissues and by the liver, one should expect very definite abnormalities in the curve of alimentary glycemia of persons who have liver disease. Because such individuals partially or totally lack one of the mechanisms that

reduces hyperglycemia, hepatic glycogen formation, the curve would presumably be excessively high or prolonged. On the other hand, the power of the tissues to remove glucose remaining intact, the arterial-venous difference should manifest itself in the normal manner." Unfortunately, however, from a diagnostic standpoint, this theoretical observation is not always borne out in fact. A normal alimentary response may be obtained in the presence of advanced hepatic disease. This is particularly true of chronic disorders such as various types of cirrhosis, passive congestion, carcinoma, and lues of the liver. This is in all probability due to the great functional reserve and remarkable regenerative power of that organ. In the acute diffuse forms of hepatic disease mentioned above significant alterations in the blood-sugar tolerance curve occur much more frequently. The type of curve obtained in typical cases of insufficiency of hepatic glycogenic function is characterized by:

1. Abnormally high rise in venous blood-sugar concentration (above 160 milligrams, Folin-Wu method).
2. The maximum concentration is attained at the end of three-fourths to one and one-half hours, and in most instances within one hour.
3. The blood-sugar level usually falls rather rapidly; returning to normal within two to three hours. Only in cases of extreme grades of hepatic insufficiency is hyperglycemia of long duration.
4. The arterial-venous difference is usually normal or, in some instances, increased.
5. The combination of a low normal or subnormal fasting blood-sugar level with a tolerance curve having the characteristics described above is highly suggestive of diminished hepatic glycogenesis.

If determinations of the respiratory quotient and serum phosphate are made at frequent intervals after the administration of glucose they will be found to change in an essentially normal manner; *i.e.*, the respiratory quotient rises and the serum phosphate falls during the period of increased glucose supply and utilization.

B. Increased Hepatic Glycogenolysis

Under this heading belong those conditions mentioned previously in connection with the consideration of the effect of hepatic glycogenolysis upon the fasting blood-sugar level. From the clinical standpoint hyperthyroidism is the most important member of this

group of disorders. The blood-sugar tolerance curve in these conditions has the following characteristics:

1. A tendency toward fasting hyperglycemia.
2. Rapid and excessive rise following the administration of glucose, the maximum concentration occurring usually within one to one and one-fourth hours.
3. Owing to the fact that tissue utilization of glucose is unimpaired the return to normal is relatively rapid, occurring usually within three hours unless the degree of elevation has been extremely high.
4. Normal or increased arterial-venous difference.

The curve closely resembles that obtained in hepatic insufficiency with the exception of the tendency toward fasting hypoglycemia in the latter as contrasted with the high normal or elevated fasting blood-sugar level in disorders associated with increased hepatic glycogenolysis. The respiratory quotient rises and the serum phosphate falls during the period of the test, evidence of the fact that tissue utilization of glucose is unimpaired.

C. Decreased Tissue Utilization

The most important clinical condition characterized by deficient utilization of glucose is diabetes mellitus, which is the most frequent disorder of carbohydrate metabolism. The fundamental defect in diabetes mellitus is a state of hypoinsulinism, resulting in a decrease in the rate of removal of glucose from blood entering the tissues. Decreased tolerance for sugar is the most characteristic phenomenon of this condition and is present regardless of the post-absorptive blood-sugar concentration. The sugar-tolerance curve in diabetes mellitus has the following characteristics:

1. Fasting hyperglycemia is present in all but very mild cases.
2. A gradual rise from 160 milligrams to an excessively high level, the degree of elevation being about proportional to the severity of the condition.
3. Following the ingestion of glucose, the maximum concentration is reached after an interval which is variable but practically always more than one hour. In general, the greater the rise, the longer is the time elapsed before the highest level is attained. In severe cases the peak may not be reached for three or more hours.
4. The most characteristic feature is the delayed return to the

postabsorptive level. A failure to return to normal at the end of three hours is usually indicative of diabetes mellitus. After reaching a maximum the blood-sugar concentration remains at a high level for a variable period, decreasing slowly to the fasting level. The higher the degree of elevation the slower is the rate of decrease, both paralleling the severity of the condition. Characteristically the curve is of the plateau rather than the peaked type.

5. The arterial-venous difference is diminished, and, in severe cases, may be almost completely obliterated.

There are other associated evidences of impaired glucose utilization. The respiratory quotient may remain at the postabsorptive level instead of exhibiting the normal increase which attends active carbohydrate storage and combustion. The serum phosphate concentration remains unchanged instead of decreasing during the period of hyperglycemia; in some cases it may be slightly increased.

Hyperpituitarism is associated with an alteration in glucose tolerance similar to that occurring in mild grades of diabetes mellitus. This is believed to be due to the antagonism existing between pituitrin and insulin, the insulin-inhibiting action of the former being exaggerated by increased pituitary secretion. The blood-sugar curves are not usually of the characteristic plateau type but rather resemble those obtained in hyperthyroidism. The respiratory quotient and serum phosphate concentration act essentially as in diabetes mellitus.

II. *Decreased Response—Increased Glucose Tolerance*

By increased tolerance is meant increased ability of the organism to handle glucose; consequently, following the ingestion of glucose the alimentary blood-sugar response is less than that observed in normal individuals. Viewed from a practical standpoint it occurs in two groups of clinical conditions:

A. Those associated with a decreased rate of hepatic glycogenolysis.

B. Those associated with an increased rate of removal of glucose from the blood (increased tissue glycogenesis and glycolysis).

A. Decreased Hepatic Glycogenolysis

Hypothyroidism and hypoadrenalinism belong under this heading. Myxedema, cretinism and Addison's disease are frequently

associated with increased sugar tolerance. The characteristics of the curves obtained in these conditions are as follows:

1. Tendency toward fasting hypoglycemia.
2. Little or no elevation of blood sugar following the ingestion of glucose, resulting in a flat type of curve.

B. Increased Tissue Utilization

This is observed typically in hyperinsulinism which may conceivably occur as a functional disturbance or, as has been reported, in association with hyperplasia, adenoma or carcinoma of the pancreatic islet cells. In some instances the condition is more properly regarded as a state of dysinsulinism rather than hyperinsulinism. The metabolic phenomena accompanying such conditions may be considered the result of a constant and increased supply of insulin instead of its periodic secretion in response to the requirements of the organism. The characteristics of the alimentary glucose response should theoretically be similar to those which attend the simultaneous administration of glucose and insulin.

1. Fasting hypoglycemia.
2. Little or no elevation of blood sugar following glucose ingestion, resulting in a flat type of curve.
3. Decrease in serum phosphate.
4. Increase in the respiratory quotient.

Strangely enough, the glucose-tolerance curves in cases of tumor of the pancreatic islet cells reported by Wilder and by Howland did not conform to this description. The blood-sugar concentration in each instance rose to excessive heights (283 and 260 milligrams respectively). This observation, suggestive of diminished sugar tolerance, was interpreted by Wilder as due to saturation of the liver with glycogen (8.25 per cent.).

Hypopituitarism, commonly occurring in late stages of pituitary tumor, is associated with increased glucose tolerance, the alimentary response being characteristically as described above; hypoglycemia (fasting) is not, however, a prominent feature although the tendency is distinctly in that direction.

III. Decreased Glucose Tolerance in Other Conditions

Decreased tolerance for glucose is commonly observed during pregnancy, particularly in the later stages. It is seldom of extreme

grade and is frequently associated with slight elevation of the fasting blood-sugar level. It is believed to be due to the disturbance of endocrine function (increased thyroid and pituitary activity) which exists during that period.

Pemberton and others have reported a decrease in sugar tolerance in about 60 per cent. of patients with arthritis, particularly if observed in an acute stage. It is believed by some that this phenomenon is dependent upon the presence of foci of infection (oral sepsis, tonsillar and sinus infection) operating through the medium of the endocrine system, either increasing hepatic glycogenolysis or suppressing the activity or production of insulin.

IV. *Abnormal Tolerance for Other Sugars*

A. *Abnormal Levulose (Fructose) Tolerance*

There has been considerable controversy regarding the efficiency of utilization of fructose by an organism in which glucose utilization is impaired, as in diabetes. As has been stated previously levulose differs from glucose in that it appears to be incapable of transformation into glycogen except by the liver. Furthermore, there is some evidence that levulose, unlike glucose, can be stored as glycogen in the liver, to a certain extent, in the absence of insulin. On the other hand, disturbances of hepatic function, perhaps incapable of significantly modifying the tolerance of the organism for glucose, may result in demonstrable alterations in levulose tolerance.

From a practical viewpoint a normal tolerance for levulose is rarely observed when the glucose tolerance is diminished. Hence the performance of the levulose tolerance test is of no clinical value in the presence of conditions such as diabetes mellitus. Its chief sphere of usefulness has been in the estimation of hepatic function in the absence of other disturbances of carbohydrate metabolism. Following the ingestion of 45 gm. of levulose, diminished capacity of the liver for transforming levulose to glycogen is evidenced by the following phenomena:

1. A rise in blood sugar of more than 35 milligrams per cent., a concentration of 135 milligrams or more being reached at some period during the performance of the test.

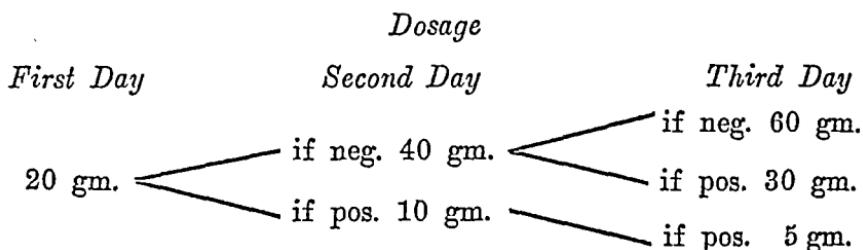
2. A delayed return to the postabsorptive level (beyond two hours).

The demonstration of a diminished levulose tolerance in the absence of evidence pointing to any disturbance of general carbohydrate metabolism is suggestive of impairment of liver function. However, negative results are commonly obtained in the presence of advanced hepatic disease especially if chronic in nature (cirrhosis, lues and malignancy of the liver, *etc.*). In more acute forms of liver disease, such as acute yellow atrophy, toxic necrosis or hepatitis associated with chloroform, arsenic, phosphorus and carbon-tetrachloride poisoning, acute catarrhal jaundice, *etc.*, positive results may be obtained. As a general rule this test is of little practical clinical value in the estimation of liver function since in most instances other evidence of functional impairment is present long before positive results are obtained. Of still less value is the procedure advocated by Strauss, in which the occurrence of fructosuria following the ingestion of 100 gm. of fructose is assumed to be indicative of liver damage. At least 10 per cent. of normal individuals respond by eliminating some fructose in the urine and many patients with hepatic disease yield negative results.

B. Abnormal Galactose Tolerance

The metabolism of galactose is similar to that of levulose in that it is converted to glycogen largely in the liver. Rowe believes that the endocrine glands, particularly the pituitary, the gonads and, to a lesser degree, the thyroid, play an important part in the metabolism of this sugar. As has been indicated the administration of 30-60 gm. of galactose appears to cause little or no elevation of blood sugar in normal individuals and no significant rise in disease states unassociated with a disturbance of general carbohydrate metabolism. Hence in the determination of galactose tolerance the procedure is limited to the qualitative and quantitative estimation of reducing substances in the urine following the administration of varying amounts of galactose. As defined by Rowe, "the tolerance level is that dose of sugar which, under standard conditions of administration, will produce uniformly a brief melituria detectable by a dependable reagent (Benedict's), while a similar dose a few grams less in amount will fail to do so." The normal threshold of tolerance for males is 80 gm. and for females 40 gm.

and is apparently independent of body weight or surface area. The following technic is outlined by Rowe.



Technic

5 A.M.	Void urine and discard
5-7 A.M.	Collect control urine (G-1)
7 A.M.	Drink galactose in 100-200 cc. cold water
7-9 A.M.	Collect test urine (G-2)
9-11 A.M.	Collect test urine (G-3)

Each test sample is examined for reducing substances by the Benedict qualitative reagent; if positive, the quantitative Benedict test is performed. Bauer regards a melituria of less than 3 gm. as of no significance.

Employed as a test of hepatic function, a decreased tolerance level is assumed to indicate impairment of liver function. It has the same clinical significance as the levulose-tolerance test and is of little practical value. The tolerance for galactose is believed to be diminished also during pregnancy and menstruation, after the menopause, in hyperpituitarism and certain pluriglandular disturbances involving gonadal dysfunction. It is raised in hypopituitarism and hypothyroidism.

**THE DISTRIBUTION OF BLOOD SUGAR BETWEEN CORPUSCLES
AND PLASMA**

In routine determinations of the sugar content of the blood, whole blood is used. Obviously, if the sugar content of corpuscles differs from that of plasma, the determination of the latter would offer a more exact index as to the glucose supply to the tissues than is afforded by the analysis of whole blood. Contrariwise, the argument has been advanced that the glucose content of the corpuscles

is comparable to that of the tissue cells generally and so is more significant than that of plasma or whole blood. Most observers report that the sugar content of plasma and that of corpuscles exhibit individual variations with varying concentrations of blood sugar. Thus John states, in an analysis of a large series of observations, "A comparison of the changes in the sugar content of the corpuscles and of the plasma in non-diabetics shows that in general the sugar content of the corpuscles is lower than that of plasma, and that as the sugar level of the plasma rises, following the ingestion of glucose, the sugar level of the corpuscles does not keep pace with it. As the sugar starts to decrease in the plasma, the corpuscles release their sugar less rapidly and we find a higher sugar level in the corpuscles. In diabetic individuals, the level of the corpuscular sugar is lower than that of the plasma sugar and only rarely does one find at the end of the test that the sugar content of the corpuscles is higher than that of the plasma. One gets the impression that in the presence of diabetes the corpuscles do not take in the sugar as rapidly as is normal." These studies suggest that in diabetes the corpuscles have a diminished capacity for taking in and for holding sugar.

Foshay believes that insulin reactions (hypoglycemia) bear no relation to the level of whole-blood sugar and that such reactions usually occur when the corpuscular glucose concentration falls below 50-55 milligrams per 100 cubic centimeters. He states that a wide difference between the plasma and corpuscular sugar levels two hours or less after the administration of insulin is indicative of a developing hypoglycemic reaction.

One criticism which may be offered to most of the reported studies in this connection is the fact that anticoagulants such as citrate and oxalate, by altering the ionic equilibrium, produce a state of abnormal permeability of the corpuscular membrane. This may conceivably alter the true distribution of sugar between the corpuscles and the plasma. Heparin may be more satisfactory as an anticoagulant. Furthermore, the cells, after being centrifuged, should not be washed as this appreciably diminishes their glucose content.

Another very pertinent fact has been emphasized by Somogyi. He pointed out the fact that in considering the distribution of glucose one must take into account the non-sugar reducing substances

which amount to about 40 milligrams in the corpuscles and 8 milligrams in plasma. Thus, the true relationship would be expressed

$$\frac{\text{Apparent corpuscular sugar minus 40}}{\text{Apparent plasma sugar minus 8}},$$

this ratio being normally approximately 0.75:1. The apparent ratio may vary considerably with variations in blood sugar while the true ratio may be unaltered. This objection is not valid if the Benedict 1928 reagent is used, since it is not reduced by non-sugar substances which react with the Folin-Wu and other commonly employed reagents.

The study of the corpuscular and plasma sugar concentrations does not, at the present time, appear to be of distinct clinical value.

BLOOD GLYCOLYSIS

The study of the rate of disappearance of glucose from blood *in vitro* first acquired distinct clinical significance when Warburg observed that the carbohydrate metabolism of tumor tissue differed from that of normal cells in that the former possesses the property of causing an increased rate of glycolysis in a glucose-containing medium. When normal whole blood, prevented from clotting by defibrination or by the addition of anticoagulants such as heparin, oxalates or citrates, is incubated at 37° C., its sugar content decreases at a practically uniform rate for four hours and is usually virtually exhausted at the end of six hours. The concentration of reducing substances at the end of this time is 10-20 milligrams per 100 cubic centimeters, representing non-glucose reducing substances.

This glycolytic process appears to be normally dependent upon the activity of the erythrocytes, as it is almost completely inhibited by their removal or after hemolysis has been produced. The number of normal leucocytes apparently has little influence, the rate of glycolysis being unaltered in the presence of leucocytosis (polymorphonuclear) of varying degree.

In polycythemia vera (erythremia), glycolysis usually occurs with increased rapidity, being complete in two to three hours. This appears to be independent of the number of red blood-cells as influenced by the administration of phenylhydrazine. In cases of

relative polycythemia glycolysis is normal. Decreased rates have been observed in pernicious anemia.

A similar increased rate of glycolysis occurs in chronic myelogenous leukemia (two to three hours) except in aleukemic stages. Some observers state that the rate is determined by the number and degree of immaturity of the leucocytes, but it may be that other factors are involved. Normal findings are usually obtained in chronic lymphatic leukemia.

There has been considerable controversy as to the relationship between the rate of glycolysis and the level of blood sugar. Some investigators report decrease glycolysis in diabetes mellitus and in hyperglycemia due to other causes. Others deny the truth of this assertion. Falcon-Lesses reports that the decrease in blood sugar is more rapid when the blood-sugar concentration is high. If one considers the amount of decrease per unit of time rather than the percentage decrease it is usually found that the rate of glycolysis is practically independent of the degree of glycemia. Insulin has no effect upon glycolytic activity.

NORMAL URINE SUGAR

In the normal individual glucose is excreted by the renal glomeruli but, constituting one of the so-called "threshold bodies," it is largely reabsorbed into the blood-stream through the tubular epithelium. A small amount, however, escaping this conservation process, is eliminated in the urine. The presence of a detectable quantity of copper-reducing substance or substances in normal urine has been recognized for many years. Benedict, Osterberg and Neuwirth found that 1.5 gm. of such substances may be eliminated in twenty-four hours and that their excretion is increased following the ingestion of food. The term "glycuresis" was applied by them to this phenomenon in substitution for the more commonly employed and misleading "glycosuria." The proportion of these reducing substances represented by glucose has been variously estimated. Neuwirth found the total quantity of reducing substances to range between 0.61 and 1.38 gm. daily, of which 0.13-0.49 gm. were fermentable and 0.37-1.02 gm. non-fermentable. Benedict believes that glucose constitutes usually not more than 25 per cent. of the urine sugar. Greenwald is of the opinion that the reducing sub-

stances excreted in normal urine are made up of poorly or non-assimilable carbohydrates and substances derived from the protein of the food and from endogenous sources. He states that the nature of the former depends on the diet (lactose from milk, pentose from fruits, caramelized sugar and dextrins) and that on ordinary diets at least 50 per cent. of urine sugars originate from food protein or endogenous sources.

The importance of the appreciation of the presence of reducing substances in the urine of normal individuals is obvious. It is important, also, to distinguish between glycuresis, a physiological, and glycosuria, usually a pathological, phenomenon. This distinction may be summarized according to the conception of Folin and Berglund, as follows: glycuresis follows every ordinary carbohydrate meal, the increase in reducing substances being independent of the amount of glucose in the blood and being due largely to the excretion of foreign unassimilable carbohydrates and carbohydrate decomposition products produced during the preparation of food. A portion of these reducing substances is represented by glucose. In a study of 700 normal individuals, Hassan found that the application of the phenylhydrazine test showed glucosazone to be present in 20-30 per cent. after one to two hours, in 12-15 per cent. after four to five hours and in 7 per cent. after twelve hours. On the other hand, the output of glucose is less after the ingestion of 50 gm. of pure glucose than following an ordinary mixed meal and the administration of as much as 200 gm. of glucose is not followed by glycosuria. After meals of bread, and particularly in concentrated urines, the ordinary reduction tests may yield positive results. The fermentation test is commonly used to distinguish between glucose and non-carbohydrate reducing substances. However, yeast sometimes fails to ferment sugar present in concentrations below 0.1 per cent. and bacteria and other agents present in the yeast negify the results if differentiation between glucose and other sugars such as lactose and maltose is attempted. Sumner states that the urine of normal individuals contains reducing substances in concentrations varying from 0.05 to 0.15 per cent. in terms of glucose; about 60 per cent. of the reduction is due to sugar. Values of 0.25 per cent. are to be considered with suspicion and 0.3 per cent. as definitely pathological.

RENAL THRESHOLD

The concept of a threshold limit of renal impermeability to glucose has served as a convenient basis for the classification of various forms of glycosuria. The renal threshold may be defined as that concentration of sugar in the blood which must be reached before an excessive quantity (above normal) of glucose is eliminated in the urine. This "threshold value" is generally assumed to be normally from 160 to 180 milligrams per 100 cubic centimeters of whole blood and 190 milligrams per 100 cubic centimeters of plasma.

There are two diametrically opposed schools of thought in this connection. The one affirms its belief in the existence of a renal threshold for glucose. Folin and Berglund, who are among the proponents of this belief, state, "Hyperglycemia definitely below the threshold does not normally produce the slightest leakage of glucose through the kidneys and normally not a trace of absorbed and circulating glucose is lost." Likewise, Joslin states, "The concept comprised in the term 'glucose threshold' is not only approximately true, but absolutely correct, however uncertain the exact figures given for the threshold may be." Benedict and Osterberg, on the other hand, say, "The more we have hunted for the elusive 'glucose threshold,' the more we feel that this is quite possibly wholly an artifact. We tend to adopt the view that the causes leading to glucose excretion by the kidney are usually the same as those leading to an increase in the blood sugar, but we question that the two latter phenomena need be always causally related." Furthermore, Folin and Berglund, while affirming their belief in the existence of a threshold for glucose and levulose, admit that there is apparently none for galactose and lactose, the elimination of which is independent of their concentration in the blood.

Whatever may be the fact of the matter, the concept of such a threshold is very useful from a clinical standpoint. It must be recognized, however, that the "threshold value," if it exists, is an extremely variable factor, varying not only in different individuals, but also in the same individual at different times. This may be due to one or more of several factors:

- I. The permeability of the kidney for sugar is dependent not

only on the level of blood sugar at that moment but also upon the duration of an existing hyperglycemia.

II. Blood and urine removed at the same time do not represent simultaneous specimens for the rate of urine formation varies as does the blood-sugar concentration during and prior to the period of urine formation.

III. The concentration of sugar in venous blood may not always be a true index of its concentration in the arterial blood supplying the kidney.

IV. The relationship between the level of sugar in the blood and its excretion in the urine varies with rising and with falling blood-sugar values. It has been found that, following the administration of glucose, its elimination in the urine began when the blood-sugar concentration was 150 milligrams per cent. and continued until it had dropped to 60 milligrams. According to Folin this is due to the fact that, prior to the excretion of the sugar, the holding capacity of the tissues, including the kidney, was exceeded, thus producing a local functional strain with the consequence that the glycosuria, once begun, does not stop when the blood sugar has fallen to the threshold value or even lower.

If one admits the practical usefulness of the concept of a renal threshold for glucose, it must be realized that the threshold level possesses a wide individual variation and is capable of extreme variation in normal individuals under certain conditions. Glycosuria has been observed in normal persons with a blood-sugar concentration of 60 milligrams per cent. (Folin-Wu) and, as in a patient under ether anesthesia reported by Macky, glycosuria may not occur in the presence of a blood-sugar level of over 350 milligrams per cent. The renal threshold is believed to be lowered during pregnancy. It is frequently elevated in nephritis, arteriosclerosis and in patients with diabetes after long periods of insulin therapy. In such cases of diabetes, blood-sugar values as high as 425 milligrams have been reported without concomitant glycosuria. With these facts in mind the statement may be made that sugar (glucose) is excreted in the urine when the level of blood sugar has risen above the normal threshold level for that individual. If the commonly accepted threshold values of 160 to 180 milligrams are considered to be normal, individuals with glycosuria may be classed

into two divisions: (1) with normal renal threshold and excessive hyperglycemia and (2) with low renal threshold and normal blood sugar (renal glycosuria).

MELITURIA

The term "melituria" is properly employed to designate the presence, in the urine, of an abnormal amount of sugar. When the sugar is glucose, the condition is termed glycosuria, when levulose, levulosuria, when pentose, pentosuria, when lactose or galactose, lactosuria and galactosuria respectively. Since all meliturias are not glycosuria, the identification of the nature of the sugar present becomes a matter of considerable moment.

TESTS FOR THE DETECTION OF SUGARS

I. Metallic Oxide Reduction Tests

The most widely used routine method for the detection of sugar in the urine is one of the copper reduction tests of which the Benedict test is perhaps the most satisfactory. The property of reducing metallic oxides in alkaline solution (copper, bismuth, mercury), possessed by certain sugars, depends upon the presence of an aldehyde or ketone group in their molecular structure. If Fehling's solution is employed, reduction may be caused by substances other than sugars, if present in sufficient concentration. Among these are uric acid, nucleoprotein and conjugate glycuronates formed after the ingestion of antipyrin, menthol, phenol, camphor, chloral, etc. Creatinine may, by dissolving cupric oxide, mask slight degrees of reduction caused by small amounts of sugar. If chloroform is used as a preservative a positive result may be obtained.

Benedict's test is much more satisfactory. It yields positive results with glucose present in as low a concentration as 0.1 per cent. The Benedict reagent is furthermore less susceptible to reduction by uric acid and chloroform.

The bismuth reduction test (Nylander) is not commonly employed. It is believed to be capable of detecting smaller quantities of glucose than the Benedict reagent but albumin produces a black color similar to that produced by sugars and so, if present, must be removed before performing the test.

The following sugars are capable of reducing metallic oxides in alkaline solution: glucose, levulose, galactose, pentose, lactose and maltose.

II. Fermentation Test

The fact that certain sugars are fermentable by yeast has been the basis for the widespread use of the fermentation test in the identification of urinary sugars. The statement is ordinarily made that glucose, levulose and galactose are fermentable by yeast and that maltose and sucrose are fermentable only after their inversion by the enzymes maltase and invertase present in the yeast. Lactose is said to be nonfermentable by ordinary bakers' yeast. One possible source of error has been indicated by Neuberg who demonstrated that yeast possesses the property of splitting off carbon dioxide from the carboxyl group of amino acids which are normally present in the urine. Another important observation has been made by Castellani and Taylor who found that ordinary bakers' yeast is not pure and usually consists of one or two species of *saccharomyces* with a contaminating Gram-positive bacillus. They showed that most cultures of so-called pure yeast ferment glucose, levulose, galactose, sucrose, maltose and, in many instances (15 per cent.), lactose. Obviously, positive differentiation of urinary sugars on the basis of this test is impossible.

Castellani has elaborated a method of differentiating various sugars on the basis of fermentation by specific fungi and gas production by specific bacteria. For example, glucose alone is fermented by *Monilia balcanica*; glucose and levulose are fermented by *Monilia krusei*; *B. coli* forms gas with lactose, whereas *B. paratyphosus* does not. The reader is referred to the work of Castellani for further details. The combined use of reduction tests and gas production by specific fungi and bacteria is of great value in the identification of urinary sugars.

III. Phenylhydrazine Reaction

This reaction depends upon the formation of crystalline osazones, the structure of which is typical, to a certain degree, for various sugars. Glucose and levulose form osazone crystals of identical structure. The identification of lactose by this test is not prac-

ticable, for lactosazone crystals, although typical, are formed with difficulty in urine. At times the determination of the melting point of these crystals is utilized as a means of differentiating the sugars but is not a procedure of practical value.

IV. Specific Rotation

The degree of rotation of polarized light, determined by means of a polariscope or polarizing saccharimeter may be employed as an aid in the identification of urinary sugars. This procedure is not frequently resorted to clinically. Furthermore, glucose and lactose cannot be differentiated by this method.

Other tests which are of value in the positive identification of urinary sugars will be dealt with in discussing the various types of melituria.

GLYCOSURIA

The term "glycosuria" signifies the excretion in the urine of abnormal amounts of glucose. Glucose may be identified in the urine on the basis of the following tests:

- (1) Positive reduction test
- (2) Fermentation with bakers' yeast
- (3) Typical glucosazone crystals with phenylhydrazine
- (4) Gas production with *Monilia balcanica* (Castellani)
- (5) Specific rotation of polarized light.

As has been indicated, the properties of reducing power and fermentation by yeast are shared by many sugars and are therefore not specific for glucose. The following criteria may be established for the positive identification of glucose:

- (1) Typical osazone crystals with phenylhydrazine in the presence of a negative Seliwanoff reaction (resorcinol-hydrochloric acid) to exclude levulose, or
- (2) Gas production with *Monilia balcanica* (Castellani), or
- (3) Specific rotation of polarized light ($+ 52.5^\circ$) in the absence of a positive mucic acid test to exclude lactose.

As has been previously indicated, the several forms of glycosuria may be conveniently classified clinically under two headings:

- I. Glycosuria unassociated with hyperglycemia, and
- II. Glycosuria associated with hyperglycemia

I. Non-hyperglycemic Glycosuria

The appearance of glucose in the urine in the presence of a normal concentration of sugar in the blood implies a lowering of the normal renal barrier to the elimination of glucose which is usually effective against blood-sugar concentrations up to 160-180 milligrams per cent. This condition may be produced experimentally by the administration of the glucoside phlorhizin. It is observed clinically in so-called renal glycosuria (renal diabetes), during pregnancy, and, as believed by some, in the condition commonly termed "alimentary glycosuria."

A. Phlorhizin Glycosuria

The administration of phlorhizin, orally, or, better, subcutaneously, is followed by glycosuria associated with a normal, and indeed, in many instances, a subnormal blood-sugar concentration. The theoretical aspects of this interesting and physiologically important condition cannot be dwelt upon except as they serve to throw light upon the possible existence of forms of glycosuria observed clinically, dependent upon factors operating locally in the kidneys. There appears to be little doubt that, as von Mering concluded, phlorhizin glycosuria is in the true sense of the term a renal glycosuria. As stated by Woodyatt, "Whatever the action of phlorhizin may prove ultimately to be, this action finds its chief expression in the cells of the kidney, and there leads to a disturbance of equilibrium, whereby the relative blood-sugar and urinary-sugar concentrations are altered in favor of the urine.

"Phlorhizin acting in the kidneys, and regardless of a possible action elsewhere, creates a void into which the blood sugar flows, and into which secondarily, as into a vortex, sugar flows from all sources of the body."

The cause of the loss of glucose from the body may be either a state of increased permeability of the kidneys to glucose or some alteration in the state of glucose in the blood plasma whereby it is enabled to pass more readily through the kidneys. The majority of the evidence points toward the former as the more likely explanation for this condition.

B. Renal Glycosuria (Renal Diabetes)

The frequency of incidence of this condition, also known as "benign" glycosuria and "diabetes innocens" is perhaps greater than is commonly supposed. Renal glycosuria is characterized by:

1. The excretion of glucose in the urine, the quantity excreted being relatively independent of the diet.
2. Normal or subnormal fasting blood-sugar concentration.
3. Normal or diminished alimentary response (normal blood-sugar tolerance curve).
4. Normal carbohydrate utilization as evidenced by determinations of respiratory quotient and serum inorganic phosphate following glucose ingestion.
5. Normal fat metabolism.

This condition is believed by many to be hereditary and familial, and it seems likely that, once developed, it persists throughout the life of the individual. Folin and Berglund are of the opinion that it is of comparatively frequent occurrence, existing in 1-2 per cent. of otherwise normal students whom they have studied. They believe, likewise, that the majority of instances of so-called "alimentary glycosuria" are, in reality, cases of renal glycosuria. The importance of its recognition depends upon its apparent harmlessness; so far as can be determined, it never results in diabetes mellitus or in any metabolic derangement whatsoever.

The essential cause of renal glycosuria is unknown. It is assumed that the permeability of the kidneys to glucose is increased, and one is tempted to draw an analogy between renal glycosuria and "orthostatic" or "adolescent" albuminuria. Autonomic instability may be a factor in its etiology as it has been shown that individuals with autonomic imbalance are hypersensitive to phlorhizin. An interesting point has been raised by Hamburger and Brinkman, who found that the renal threshold for glucose could be raised or lowered by increasing or decreasing the ratio between calcium and sodium and potassium in the perfusing fluid. Cammidge goes so far as to state that renal glycosuria is always associated with an absolute, and not merely a relative, reduction in the proportion of calcium in the blood plasma.

C. Glycosuria of Pregnancy

Glycosuria, occurring during a normal, uncomplicated pregnancy appears to be due to lowering of the renal threshold since it is associated with no elevation of blood sugar. It is observed in as many as 10-15 per cent. of all normal pregnant women, particularly in the later months and more frequently in primigravidae than in multigravidae. Pregnancy glycosuria is ascribed by some observers to a decreased carbohydrate tolerance resulting from the physiologic hypertrophy of the pituitary gland which occurs during that period. It may, however, be due, as was mentioned in connection with renal glycosuria, to the decrease in serum calcium which is a common feature of the later months of parturition. Lactose, contrary to popular opinion, is never normally present in the urine during pregnancy, physiologic lactosuria occurring only during the period of lactation.

D. "Alimentary" Glycosuria

Opinion is divided regarding the metabolic status of so-called "alimentary" glycosuria. The term is employed to designate the urinary excretion of glucose by certain apparently normal individuals after the ingestion of excessive amounts of cane-sugar, glucose or, at times, starch. It is evident that the occurrence of glycosuria under such circumstances must be due either to a lowering of the renal threshold for glucose or to the absorption of glucose from the intestine at a rate too rapid to allow of its adequate removal from the circulation by the liver.

Woodyatt and his associates have shown that the normal individual can utilize glucose injected intravenously in amounts up to 0.8 gram per kilogram of body weight per hour; when this rate is exceeded glycosuria occurs. It has also been demonstrated that the absorption of glucose from the intestine proceeds normally at a maximum rate of 1.8 gm. per kilogram of body weight per hour, regardless, within wide limits, of the quantity of sugar ingested. Consequently, if the liver removes a minimum of 1.0 gm. per kilogram per hour, allowing 0.8 gm. to pass into the general circulation, glycosuria should not be expected to occur in normal individuals. In the absence of abnormality of hepatic or tissue glycogenic function, alimentary glycosuria might be explained upon the basis of increased permeability of the intestinal mucosa for glucose, result-

ing in its absorption at a rate more rapid than can be adequately handled by the liver; it therefore reaches the tissues, including the kidneys, at an excessively high rate with the result that a portion is eliminated in the urine. This hypothesis does not necessarily imply the existence of venous hyperglycemia, for, tissue utilization being unimpaired, slight grades of arterial hyperglycemia may possibly be corrected and the concentration of glucose in blood leaving the tissues be within normal limits. This has been borne out by Friedenson in studies of capillary and venous blood-sugar tolerance curves in benign glycosuria. Some authorities believe that alimentary glycosuria, in most instances, is in reality renal glycosuria. Others maintain that many such cases are dependent upon some disturbance of intermediary carbohydrate metabolism originating in the liver, endocrine glands or tissues (muscles). No such disturbance can be satisfactorily demonstrated in most cases.

II. *Hyperglycemic Glycosuria*

The occurrence of glycosuria in association with hyperglycemia is readily understood. If one accepts the normal renal threshold value as being 160-180 milligrams of glucose per 100 cubic centimeters of blood, the elimination of glucose in the urine may be expected in the presence of higher blood-sugar levels. The fact must be kept in mind, however, that the renal threshold may exhibit rather wide variations in different individuals and under different conditions. Obviously, the causes of hyperglycemia are potential causes of glycosuria. These include the following:

1. Diabetes mellitus

Diabetes mellitus is the most frequently observed individual cause of glycosuria dependent upon hyperglycemia. The view that glycosuria always indicates diabetes mellitus is, however, erroneous, even in the presence of hyperglycemia. John, in an illuminating analysis of 398 patients with glycosuria, found that only approximately 37 per cent. were true diabetics. Diabetes was the cause of glycosuria in only 29.9 per cent. of individuals under twenty years of age presenting this symptom. As has been mentioned previously, glycosuria is not uncommon in the later months of pregnancy. Its occurrence in the early months should lead to a rigid investigation of the possibility of the existence of diabetes mellitus. The differen-

tial diagnosis between diabetes and other conditions causing hyperglycemic glycosuria entails an investigation of blood-sugar tolerance curves, the arterial-venous blood-sugar difference, the serum phosphate curve and respiratory quotient variations following glucose ingestion, the plasma cholesterol concentration and the basal metabolic rate (hyperthyroidism). Further details will be considered in the section on diabetes mellitus.

2. Hyperthyroidism

Glycosuria occurs in 25-35 per cent. of patients with hyperthyroidism. Its incidence is somewhat higher in cases of primary (exophthalmic goiter) than secondary hyperthyroidism (toxic adenoma). Associated with manifestations of hyperthyroidism, particularly an increase in the basal metabolic rate, it is usually readily distinguishable from other causes of glycosuria and hyperglycemia. It must be recognized that diabetes and hyperthyroidism may co-exist and that hyperthyroidism is likely to act as a predisposing cause of diabetes.

3. Hyperpituitarism (acromegaly)

4. Hyperadrenalinism

Excessive mental strain and emotional excitement may be followed by glycosuria.

5. Severe exercise, not greatly prolonged

6. Increased intracranial pressure as in brain tumor, cerebral hemorrhage, fractured skull, etc.

7. Vascular hypertension, chronic hepatic disease, chronic nephritis, and nephrosis are at times accompanied by glycosuria

8. Following ether anesthesia, asphyxia (mechanical, nitrous oxide and ethylene anesthesia), and acidosis due to other factors

LEVULOSURIA

Levulose (fructose) reduces metallic oxides in alkaline solution, is fermentable by bakers' yeast and yields an osazone with phenylhydrazine which is structurally identical with glucosazone. Levulose may be identified in the urine by the following methods:

1. Gas production with *Monilia krusei* but not with *Monilia balcanica*, to exclude glucose.
2. Characteristic osazone crystals and positive Seliwanoff (resorcinol-HCl) or Borchardt reaction, to exclude glucose. The pres-

ence of nitrites and indican in excess interferes with the development of the characteristic yellow color of Borchardt's reaction. Glucose, in large amount (2 per cent.), may yield a positive Seliwanoff reaction.

3. Rotation of polarized light to the left in the absence of other levorotatory substances as conjugate glycuronates and betahydroxybutyric acid.

Levulose may appear in the urine under the following circumstances:

1. In severe cases of diabetes mellitus, always in association with glucose.

2. Alimentary levulosuria, following the ingestion of large quantities of levulose, particularly in patients with hepatic insufficiency. This has been utilized as a test of hepatic function but is unsatisfactory; approximately 10 per cent. of normal individuals eliminate levulose in the urine following the ingestion of 100 gm. of levulose.

3. Essential levulosuria, implying the occurrence of levulosuria in the absence of the above-mentioned factors, is a rare condition. A few cases have been reported in which there was a total absence of tolerance for levulose, the sugar being eliminated if any whatsoever was ingested. Heeres and Vos state that regardless of the amount ingested, about 14 per cent. is eliminated. Insulin has no influence upon this condition; no rise in the respiratory quotient follows the administration of levulose to such individuals, indicating failure of utilization of that sugar. It is said that rectal administration produces more severe levulosuria than when given by mouth.

PENTOSURIA

Pentoses reduce metallic oxides in alkaline solution and are non-fermentable by bakers' yeast. They may be identified in the urine by the following methods:

1. Bial reaction (Orcinol-HCl)
2. Positive Benedict reaction and negative fermentation test with bakers' yeast in the absence of lactose and non-sugar reducing substances (conjugate glycuronates)
3. Characteristic pentosazone crystals with phenylhydrazine

4. Positive Benedict reaction, gas production with *B. coli communis* and *B. paratyphosus B.* (to exclude lactose) and no fermentation by *Monilia tropicalis* (to exclude galactose)

Pentose may appear in the urine under the following circumstances:

1. Alimentary pentosuria

This is a temporary condition, occurring in normal individuals after the ingestion of large quantities of fruits which have a high pentose content (prunes, cherries, grapes, plums). It is of no clinical significance apart from the fact that it may be mistaken for glycosuria because of a positive copper-reduction test.

2. In diabetes mellitus

3. Essential pentosuria (chronic pentosuria)

This is a relatively rare and extremely interesting condition which is analogous to essential levulosuria. Pentoses, usually the optically inactive form of arabinose, are more or less constantly present in the urine, the quantity excreted bearing no relation to the amount ingested. It is of no known clinical significance, since the utilization of other carbohydrates is unimpaired. It appears to be familial and hereditary in nature. As in the case of alimentary pentosuria, its chief importance lies in the possibility of mistaking it for glycosuria.

LACTOSURIA

Lactose reduces metallic oxides in alkaline solution (Benedict, Fehling, etc.) and, in about 15 per cent. of cases, is fermented by bakers' yeast. It may be identified in the urine by the following methods:

1. Positive Benedict test, gas production with *B. coli communis* and no gas production with *B. paratyphosus* (to exclude pentose).

2. Positive mucic acid test and negative phloroglucinol-HCl reaction (Tollens) to exclude galactose.

3. Characteristic lactosazone crystals with phenylhydrazine. This test is usually unsatisfactory.

4. If positive Benedict test and no fermentation with bakers' yeast, negative Bial test to exclude pentose.

Lactosuria occurs in a considerable proportion of women during the period of lactation. It never occurs normally during preg-

nancy. The lactosuria of lactation must be regarded as physiologic and has no apparent clinical significance.

GALACTOSURIA

Galactose reduces metallic oxides in alkaline solution and is fermented by most samples of bakers' yeast, although usually not so actively as are glucose and fructose. It may be identified in the urine by the following methods:

1. Positive mucic acid test to exclude all other reducing substances except lactose and positive phloroglucinol-HCl reaction (Tollens) to exclude lactose.
2. Positive Tollens reaction and no absorption bands upon spectroscopic examination (to exclude pentose and glycuronic acid).

Galactosuria is not frequently observed except following the ingestion of supertolerance doses of galactose. It has been found to occur in nursing infants in association with derangements of gastrointestinal function.

THE ANTIFREEZE METHANOL HAZARD*

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THE wolf in the clothing of the sheep still finds his counterpart in the world of modern commercial products. An old chemical of well-known danger to man, methanol, that is, wood alcohol, now stalks among us wearing the fleece of new trade names. The extent of the danger inherent in wood alcohol when used industrially is well known to chemists, to physicians and to all students of industrial poisons. An authority among these last, Dr. Alice Hamilton, has termed methyl alcohol especially an American poison, stating with regard to methanol poisoning that, "There have been more industrial cases in the United States than in any other country."

This old danger now menaces the general public through its recent extensive use as an antifreeze mixture for automobile radiators. In previous years ordinary denatured alcohol containing less than 5 per cent. of poisonous wood alcohol was used in radiators of automobiles to prevent freezing. This small amount of the crude wood product did not develop into a health menace to the garage worker nor to the automobilist. But during the past few years the market price of methanol has been cut in half. It is now produced synthetically at the cost of only twenty cents a gallon. The total output for 1930 is estimated at from seven to ten million gallons. While its largest sale at present is reported to be in the production of formaldehyde it has also found an outlet in the products now sold as freeze preventives, while its concentration has been raised from the former 5 per cent. to 76.5 per cent. Ordinarily from 1 to 2½ gallons of the antifreeze mixture are used in the radiator, bringing the present average concentration to from 30 to 45 per cent. This is the proportion recommended by the manufacturers, but many automobilists are using larger amounts, creating a stronger mixture which brings the concentration to about 60 per cent. Then, too, the radiator capacity of the automobile may vary from 10 to 22

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quarts, yet the recommended proportion or percentage of methanol remaining constant, it naturally follows that the total amount of methanol to which the consumer is exposed is much greater in the case of large radiators than in the case of small ones.

These new antifreeze mixtures have been rendered marketable by creating for them new trade names, thus concealing the presence of their high content of wood alcohol, a name which, even to the general public, has come to have an ominous sound. Automobilists have been further misled by the frequent labelling of the product as "a completely denaturized alcohol" or as "94 per cent. alcohol," omitting the word *wood* or by the chemical names of methyl alcohol or methanol. The device of coining trade names is an old method of obscuring the presence of wood alcohol, the knowledge of which would impair its sale. Thirty years ago the Society for the Prevention of Blindness strongly opposed the use of the fanciful names of Columbian Spirits and Colonial Spirits as trade names for wood alcohol used in industry. The need for similar efforts has reappeared.

In December, 1930, the United States Bureau of Mines issued an Information Circular (No. 6415) pertaining to "The Effect of Methanol Antifreeze on Health." The investigation is being made by the Bureau at the request and with the assistance of the chemical industry interested in the manufacture and marketing of methanol. The whole trend of this circular is to minimize the danger arising from the use of wood alcohol as an antifreeze agent. From observations made to date this report concludes that, "There is no danger of poisoning from the reasonable use of methanol as an antifreeze for automobile radiators."

The effect of such an article is to be regretted. While it admits that only a preliminary study has been made, this fact will doubtless be overlooked by distributors of the methanol product and by the general public which ordinarily looks upon government publications as authoritative and final.

The studies up to date, upon which the conclusions are drawn, were made upon thirty-six men working in four plants engaged in the manufacture of methanol. The men had worked in these plants for periods varying from a few months to fifteen years. It is not stated what proportion of the men had been employed for the longer

periods of time. Did the thirty-six men studied constitute the entire number of persons exposed to the methanol in those plants at that time? And what was the labor turnover in those plants? Had it been affected by any health injuries which might be attributed to the exposure to methanol? The examination of these men included a general physical examination, with laboratory tests on the blood and urine. The eyes particularly were examined. Mention is not made of any analyses of the expired air for its methanol content. A thorough study of the hazards of the industry requires an investigation of these problems and all quantitative data should be presented before conclusions are published—even in a preliminary report.

The Bureau of Mines is continuing its investigation, yet no plans are mentioned for studies on the effect of methanol fumes on children, pregnant women and other persons who by reason of illness may be particularly sensitive to toxic gases. Yet such persons form a large proportion of the automobile riding public and would be exposed to the hazards of the methanol fumes. The hazards for children especially should be studied. It is well known that the metabolic rate, volume of breathing and the rate of circulation in children are proportionately greater than in the adult. These facts render children more susceptible than adults to any toxic gas or vapor. Therefore, investigations which show no apparent injury suffered by adult healthy workmen when exposed to the fumes of wood alcohol are not conclusive for children. Laboratory studies of the effects of the methanol fumes should be made upon young as well as old animals before the antifreeze mixtures are declared harmless.

Thus far we have considered the dangers inherent in wood-alcohol by reason of its new use. We must not overlook the dangers involved in its *misuse*. That is—will not its increased use in the radiators of automobiles, its wider distribution, tend also to increase the number of cases of poisoning by attempts to convert into a beverage? On this point the Bureau of Mines circular is emphatic in stating that “all methanol whether made by wood distillation methods or synthetic methods, or whether it is crude, refined or highly purified, is poisonous when taken internally.” The government report then recommends that “all antifreeze methanol

be brightly colored" to avoid such misuse. This recommendation, however, will hardly be followed by all producers until legislation requires it of them. Were methanol obtainable only in drug stores it would be promptly included under the laws governing the sale of all poisons, especially because it has a taste and odor somewhat similar to grain alcohol.

There are few poisons whose effects are so insidious and so difficult to diagnose in their pre-acute stage as methanol. The high degree of toxicity of methanol appears to be dependent upon its extremely slow destruction in and elimination from the body, continued exposure consequently resulting in a marked cumulative effect. In many fatal cases no definite symptoms develop for from twenty-four to thirty-six hours. The manifestations of acute poisoning are characterized by the combination of gastro-intestinal and visual disturbances. Abdominal pain, nausea and vomiting are rapidly followed by blurring of vision, partial or total blindness, coma, convulsions and even death from respiratory failure. The visual disturbance is apparently dependent upon optic nerve atrophy and consists of variability in visual acuity, concentric contraction of the color and form fields, pain and tenderness of the eyeballs, dilated sluggish pupils and muscular weakness resulting in diplopia and ptosis. The manifestations of chronic methanol poisoning are much more insidious and not so obvious. The gastro-intestinal symptoms may be so slight as to be completely overlooked and the condition may only be suspected by the occurrence of gradually progressive visual disturbances of the nature described above in individuals exposed to the poison.

In spite of the fact that certain large producers of methanol antifreeze voluntarily label their containers so as to warn against its misuse, so important a menace to public health should not be left to the voluntary action of those who are interested primarily in the sale of the product. Legislation requiring the correct and conspicuous labelling of all methanol containers with the word "Poison" is an urgent necessity. Such labelling would help to minimize the danger of its being taken as a beverage. There would still remain, however, the danger involved in inhaling its vapors. The Bureau of Mines investigators do state, however, that "continued exposure to high concentration will cause serious poisoning."

We have been severely criticized by medico-legal authorities of Europe for permitting an industry to expose the public to a poison that may injure thousands until such time as the slow wheels of legislation will have been set in motion to prevent further harm. Similar criticism of our American tendency to delay governmental control of health hazards is expressed in an editorial of the *Journal of the American Medical Association* concerning the new hazards from toxic gases. The editor points out that "the American people are beginning to be protected as concerns the food they take into their stomachs. They have only inadequate protection of the air they take into their lungs." Even where laboratory studies have revealed these hazards, such knowledge is not self-enforcing and government ordinances are necessary to protect the public from its own ignorance of the danger. Therefore a maximum permissible concentration of methanol for this new use in the radiators of automobiles should be established, such concentration being determined by thorough studies made with reference to all types of persons likely to be exposed to the vapors. The general public should not constitute an experimental laboratory for the testing out of a new hazard for the sake of a new industry.

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Clinical Papers from the Medical Department of Emory University, Atlanta, Georgia

TREATMENT OF PULMONARY TUBERCULOSIS BY SURGICAL COLLAPSE

By FRANK K. BOLAND, M.D.

Atlanta, Georgia

THROUGH knowledge of the cause and prevention of tuberculosis great progress has been made in decreasing the morbidity and mortality of this universal, devastating disease. While the aid of surgery has been invoked for a long time in treating the disease as manifested in other organs, only recently has such therapy been employed in combating tuberculosis of the lungs.

The feature of the treatment which has contributed more than anything else to the successful medical management of pulmonary tuberculosis is rest. By producing more complete and permanent rest of the lungs, treatment by surgical collapse is furnishing valuable assistance in controlling the malady, whereby the lives of many sufferers are being saved and the lives of others are being prolonged and made more comfortable.

Rest is induced through surgical collapse by one of four principal methods: (1) artificial pneumothorax; (2) extrapleural pneumolysis; (3) phrenicectomy; and (4) extrapleural thoracoplasty. Artificial pneumothorax is the oldest, simplest and safest means of collapsing the lung, and should always be tried before attempting more radical surgery. The efficacy of the procedure usually depends upon the absence of pleural adhesions. The existence of adhesions interferes with satisfactory collapse when air is introduced into the pleural cavity. Such adhesions may be divided by cauterization through a thoracoscope, as suggested by Jacobaeus, and as practiced so successfully in this country by Mat-

son, of Portland, Oregon. The risk of this step, however, appears so great that at the present time it is not generally advocated.

It may be stated as a rule that so long as artificial pneumothorax gives satisfactory results, a change in treatment is not advisable. The method belongs almost exclusively to the medical attendant, but should always be practiced under strict aseptic precautions. The second method of collapse, extrapleural pneumolysis, has been used by only a limited number of surgeons, and appears to have but few indications.

Phrenicectomy and extrapleural thoracoplasty are the agents of collapse which enjoy the widest application. Other names have been attached to the operation for excision of a portion of the phrenic nerve to effect paralysis of the diaphragm, but none seems better than phrenicectomy. The success of the procedure is dependent upon the extent of the nerve and its accessory filaments which can be removed. Simple section causes only temporary paralysis of the muscle, since sooner or later the nerve will regenerate if no portion of it is excised. Freezing the nerve has been done for the relief of intractable hiccough, and section is recommended in the treatment of bronchiectasis.

Phrenicectomy.—Phrenicectomy has been described so often in recent literature that every step of the operation will not be given. A few points deserve special mention. A vertical incision, parallel with the posterior border of the sternomastoid muscle, gives the best exposure; a horizontal incision, parallel with the clavicle, leaves a less conspicuous scar. The position of the patient on the table is important. The head should be turned only slightly away from the nerve which is to be exposed. If the head is turned too far, the scalenus anticus muscle may be rotated on itself, and the structures on its lateral side brought into view. Such structures will be branches of the brachial plexus. The purpose is to expose the anterior surface of the muscle, upon which the phrenic nerve usually is found without difficulty. It is a nerve of considerable size, generally lying under a pad of fat, somewhat imbedded in the muscle, and running diagonally downward and inward.

The operation needs only a local anesthetic, and when the operator comes to identify the nerve he is glad the patient is awake, be-

cause as soon as the nerve is picked up the patient complains of pain in the corresponding shoulder. If it is a branch of the brachial plexus, the pain usually is referred lower down the arm. The nerve should be well anesthetized before being cut, since failure to do this sometimes causes shock. Evulsion is carried out slowly and carefully, by wrapping the nerve around the point of a small curved hemostat. If a long section of the nerve is being delivered, the patient may complain that his whole chest is coming out, a sensation probably due to the pull on the diaphragm. The pain rarely is so great as to require treatment.

In our experience, unless as much as 8 centimeters of the nerve is excised, the results of the operation are disappointing. The removal of at least this much of the nerve is necessary in order to realize any appreciable rise in the level of the diaphragm. The degree of collapse of the lung depends upon the height to which the diaphragm is elevated. Perhaps a more important factor in the outcome of the operation than the length of nerve evulsed is the removal of accessory branches. This is a matter beyond the control of the operator. When the nerve breaks the operation is over. There is no opportunity to excise more of it, or to be sure that all accessory branches are gone. These things account for the variable results in phrenicectomy. In a few cases brilliant results have been reported. Such cases must have had complete paralysis of the corresponding half of the diaphragm. Davies quotes Pruder as reporting a case in which the diaphragm rose as high as the second rib.

Should blood ooze up along the nerve during evulsion it probably means that a vein is caught between the main nerve and a branch. The subclavian vein has been torn in this manner. Two other factors appear to affect the results of the operation. Some authorities deny that diaphragmatic adhesions may prevent rise of the diaphragm after evulsion of the nerve, but our experience indicates that such may be the case. Before performing the operation, failure was predicted in several of our cases on account of the diaphragmatic adhesions, and the predictions proved to be correct. Another more common cause of poor results in phrenicectomy is the presence in the lung of cavities with dense, unyielding walls, which will not collapse following considerable rise of the diaphragm.

Case Report.—The roentgenograms (Figs. 1 and 2) are shown illustrating the marked rise of the diaphragm following the excision of 20 centimeters of the phrenic nerve. Marked diminution in the diameter of a thick-walled cavity also is demonstrated. The patient had been sick two years when she was operated upon July 11, 1930. Every symptom has been helped. One of the first signs of improvement noticed in these cases is the increased ease with which sputum is raised. Such improvement was present immediately in this patient; the sputum became negative for tubercle bacilli, cough was less, fever disappeared, the weight increased, and in every way the patient felt and looked better.

Altogether, she appears to have derived the maximum amount of benefit possible from phrenicectomy at the time it was performed. Other factors being equal, the degree of improvement following successful phrenicectomy depends upon the pathology present when the operation is done, and the extent of pathology bears a direct ratio to the length of time the disease has existed. If this young woman could have had such a phrenic nerve evulsion a year or eighteen months earlier, with the resultant rise of the diaphragm and lung collapse, the benefit would have been far greater. Indeed, it is possible to conceive of a cure following very early phrenicectomy in certain cases, and such cures have been reported.

The maximum height of elevation of the diaphragm was attained in this case in two months; in other cases the diaphragm may continue to rise for a longer time. This patient is still under strict sanatorium treatment, and is getting better. Certainly the prognosis is improved after phrenicectomy. She may become a candidate for extrapleural thoracoplasty. Preparation for this operation is one of the chief indications for phrenicectomy.

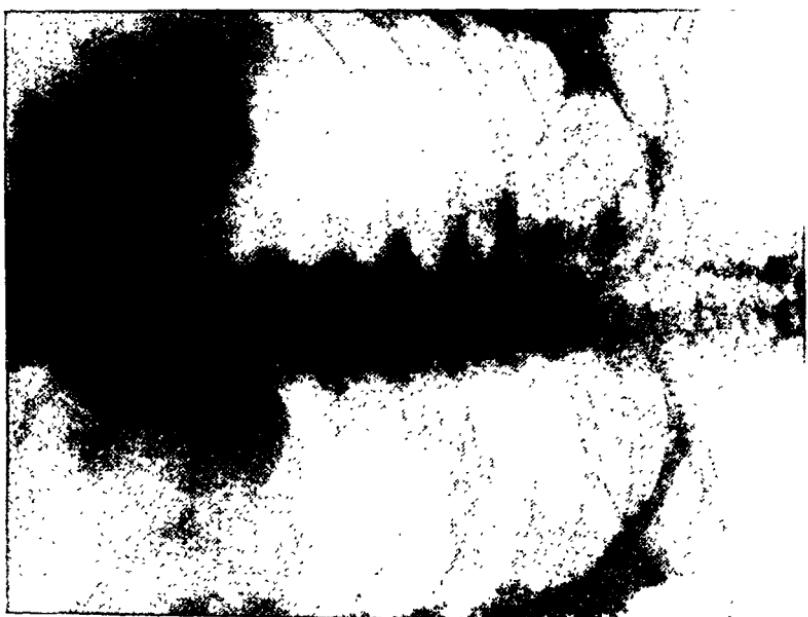
Extrapleural Thoracoplasty.—As this high-sounding name implies, it means a plastic operation upon the chest outside of the pleural cavity. Perhaps a simpler expression may be forthcoming. The object of the procedure is to collapse the chest wall to such an extent as to compress the diseased lung completely and permanently, and thus destroy all suppurating spaces, put the lung at rest, and reduce it to a non-functioning fibrous mass. Naturally, an operation of such magnitude would not be performed upon a lung that had not already ceased to function for the good of the patient, but is acting only as a warehouse of infection to consummate in premature death. Again, the operation is absolutely contraindicated unless the opposite lung is practically free of the disease. To find the opposite lung perfectly normal cannot be expected.

The operation is plastic in that sufficiently long segments of the upper eleven ribs are removed to reduce materially the capacity of the corresponding thoracic cavity. It is remarkable how little deformity results in adults. In children, in whom thoracoplasty rarely

FIG. 1.



FIG. 2.



CASE I.—Showing pulmonary tuberculosis of left lung with large cavity in upper lobe. Note low position of left diaphragm. Cause of elevation of right diaphragm not known.

CASE I.—Showing elevation of left diaphragm after excision of 20 centimeters of phrenic nerve. Note reduced size of cavity as compared with Fig. 1.

Fig. 3.



well-advanced tuberculosis of right lung with mediastinum well drawn to the affected side.

Fig. 4.



Case III.—Showing tuberculosis of left lung with trachea practically in mid-line.

is indicated, deformity may be pronounced. The ribs are removed subperiosteally, and the whole operation must be done extrapleurally. Opening the pleura is dangerous on account of the likelihood of inducing empyema.

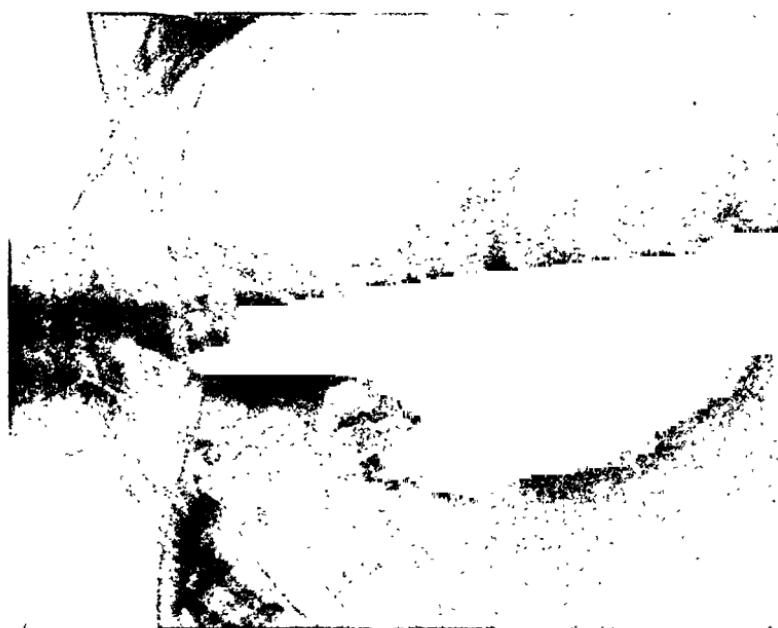
The success of extrapleural thoracoplasty depends upon performing the right operation upon the right patient at the right time. By the right operation is meant especially not doing too much at one sitting. While probably more complete collapse is obtained by finishing the operation at one sitting, few tuberculous patients are prepared to withstand such an extensive procedure, and the mortality is much higher than when the program is carried out in two or more stages.

While one would prefer to use local anesthesia exclusively in these cases, many of the patients, on account of nervousness, are not good subjects for local anesthesia, and gas or ether has to be added. One of our patients did well under novocain, preceded by sodium amytal. With the patient in the prone or semiprone position, the incision is begun just below the middle of the clavicle and is extended downward midway between the spinous processes and the edge of the scapula. For the first-stage operation the incision stops at the level of the sixth or seventh rib; for the second stage the incision is continued down to the level of the tenth rib. The ribs are exposed rapidly by cutting through the muscles, which form a much thicker mass in the upper half of the wound than in the lower half. There are so many bleeding points to be caught in the upper half that the use of the electrocautery coagulating knife expedites the work materially.

Some authorities believe that the first stage of the operation should include removal of the upper ribs, while others think the lower ribs should be taken first. As a logical solution of the problem, if the disease is more advanced in the upper half of the lung, the operation should begin above, whereas, if the lower half is more diseased, the operation should begin below. Eventualities may prevent more than the first stage ever being done, so that it is well to make sure of collapsing the worst part of the affected organ.

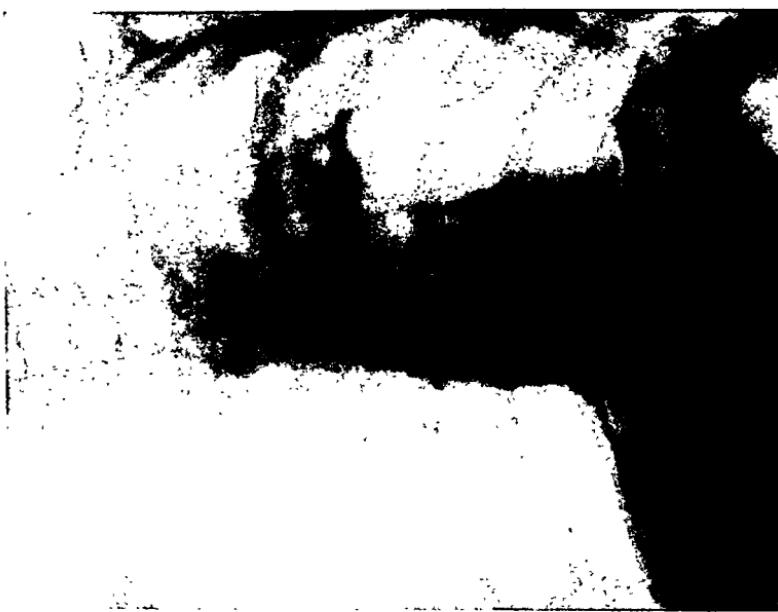
We have found it convenient first to excise about 3 inches of the third rib, and 2 inches of the second rib, after which it becomes

FIG. 3.



Case II.—Showing well-advanced tuberculosis of right lung with trachea and mediastinum well drawn to the affected side.

FIG. 4.



Case III.—Showing tuberculosis of left lung with trachea practically in mid-line.

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We have found it convenient first to excise about 3 inches of the third rib, and 2 inches of the second rib, after which it becomes

easier to expose and remove about an inch of the deeply imbedded first rib. This may conclude the first sitting of the operation, or usually it is safe to excise also 4 or 5 inches of the fourth and fifth ribs. The number of sittings depends upon the reaction of the patient. No chances must be taken. It is better to quit voluntarily than to be forced to do so. The most important part of the rib to remove is the portion nearest the transverse process of the vertebra. Excision should extend as closely as possible to this point. By this means the greatest collapse is obtained. Removal of long rib sections in the mid-portion of the bone will produce but little collapse. Not more than ten days should elapse between sittings. Five or 6 inches of the sixth, seventh and eighth ribs are excised, and then shorter sections through the eleventh.

While thoracoplasty does not present much technical difficulty to the experienced surgeon, it is by all means a major operation, and should not be undertaken without most positive indications. The right patient and the right time to operate must be decided by the internist. Many victims of the disease, learning of the success of surgical treatment, beg for operations, but the advisability of extra-pleural thoracoplasty must be determined by the physician and not by the patient. While thorough study of the case by physical signs cannot be neglected, the value of roentgenology must be recognized, especially in the consideration of performing thoracoplasty. The roentgenogram must demonstrate fibrous and scar-tissue formation as shown by the mediastinum and its contents being drawn toward the affected side. This condition is well manifested by the displaced position of the trachea.

Such fixation of the mediastinum usually insures against collapse of the heart and mediastinal flutter when the lung is collapsed. An already weakened heart, thus affected, is the commonest cause of early death in this operation. Shock, hemorrhage and infection, though they may be alarming, rarely are responsible for a fatal result. Pneumonia and other pulmonary complications seldom cause mortality.

Case Reports.—However, the Roentgen picture of mediastinal fixation does not always promise a favorable outcome. Fig. 3 shows a case of well-advanced unilateral pulmonary tuberculosis with the trachea well drawn toward the side of disease. The patient had been sick three and a half years, and recently

FIG. 5.

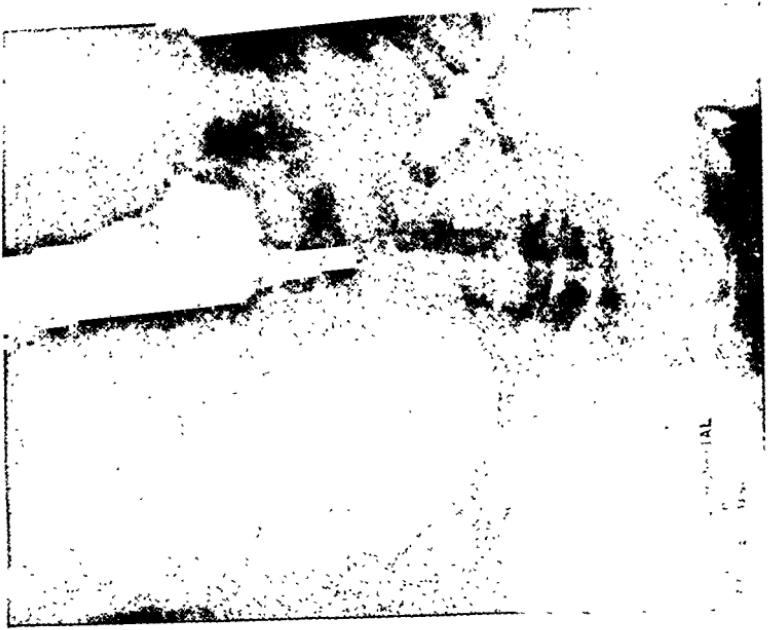
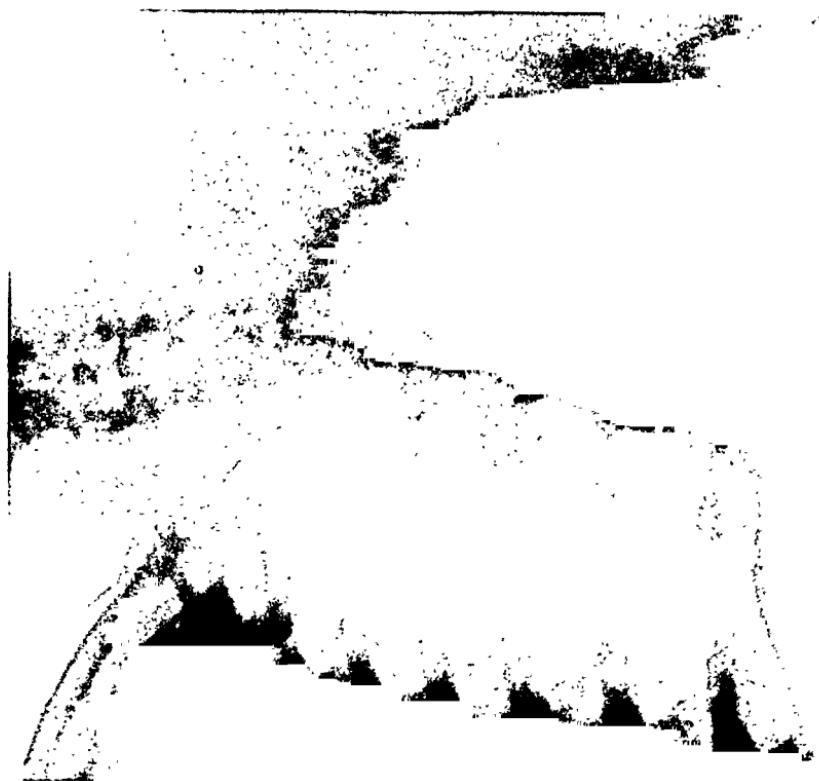


FIG. 6.



Case III.—Roentgenogram taken after first stage of thoracoplasty. Case IV.—Showing tuberculosis of left lung with trachea well drawn to the affected side.

FIG. 7.



CASE IV.—After completing thoracoplasty, trachea being in mid-line.

FIG. 8.



CASE V.—Showing scar three years after operation.
Note lack of deformity.

had had serious hemorrhages. Artificial pneumothorax was attempted without success, and it was thought that phrenicectomy would do but little good on account of diaphragmatic adhesions. With the approval of medical men in attendance, extrapleural thoracoplasty was performed in two stages, ten days apart, with satisfactory immediate postoperative results. The patient appeared to be reacting normally from the operations until the fourth day after the second stage, when his heart suddenly became weak and rapid, and he died a few hours later. There was no evidence of pulmonary complications. Unfortunately no autopsy was obtained.

On the other hand, Fig. 4 is the roentgenogram of a fairly unilateral case in which the trachea is in the midline. The patient had been sick four years, and artificial pneumothorax was a failure. Nine centimeters of the phrenic nerve were excised without producing much elevation of the diaphragm. In August, 1930, extrapleural thoracoplasty was performed in two stages, and apparently the patient is now on the way to comparative recovery. Her anemia has disappeared, and all symptoms have improved, although occasionally there are bacilli in the sputum. Fig. 5 is the roentgen film after the first stage of the thoracoplasty, showing partial collapse. A later film has not been made.

Fig. 6 shows the chest of a woman who had been a tuberculous subject for seven years. The trachea is drawn toward the affected side. Artificial pneumothorax proved ineffective and phrenicectomy produced little result. Thoracoplasty was done in two stages in 1927, and apparently the patient is now well. She has grown fat; occasionally she has some cough and sputum, but she has no fever, and all examinations for tubercle bacilli are negative. She is now able to earn a living. Fig. 7 shows the collapsed chest as it is today, and Fig. 8 is a photograph of the patient's back demonstrating the scar and lack of deformity.

While the treatment of pulmonary tuberculosis by surgical collapse still leaves much to be desired, the results have been encouraging, and should stimulate further efforts in the selection of the right cases for operation, and in the improvement of the technic. The patient should always be under the watchful care of competent phthisiologists, before and after surgical treatment, and ill-advised operating by overzealous surgeons should be discouraged. It is believed that the greatest advance in the therapy of pulmonary tuberculosis will be brought about by the use of surgical collapse earlier in the disease.

A METHOD OF TREATMENT OF HEMOTHORAX

By J. D. MARTIN, M.D.
Atlanta, Georgia

FOR many years penetrating wounds of the chest have been the subject of much discussion. During the late war much opportunity was afforded for an interpretation and treatment of this condition. A case of gunshot wound of chest with hemopneumothorax is presented to show the usual method of treatment in this clinic.

A negro man of twenty-seven was admitted to the surgical service of the Emory Division of the Grady Hospital November 16, 1930, after having been shot by a No. 44 pistol. The bullet entered the left side of the chest posteriorly on a level with the ninth rib about $1\frac{1}{2}$ inches from the spine. On admission he exhibited signs of profound shock. There was slight crepitation in the region of the bullet wound and evidence of both air and fluid in the chest, which was verified by roentgenogram. The course of the bullet was outlined by finding small fragments as it passed upward and into the lung, passing under left clavicle and stopping under left mandible.

At this time there was no evidence of an injury in the neck, but the next day there was a marked swelling of the neck, face, and scalp on the left side. Surrounding and accompanying this swelling was a marked ecchymosis and subcutaneous emphysema which extended well down on the anterior thoracic wall (Fig. 1).

Dyspnea became quite marked and it was noted that the tonsilar fauces and the posterior pharyngeal wall on the left side were also ecchymotic. There was a question at this time of relieving this dyspnea by tracheotomy or incision of the hematoma, but fortunately the dyspnea was transient. Definite signs of fluid and air were still present, increasing to the extent that the heart was displaced until its right border was 6 centimeters from the mid-sternal line. The left border of the heart was not determined due to the marked hyperresonant note over the entire left chest. An electrocardiogram taken at this time showed no changes.

Forty-eight hours after the injury roentgenographic examination revealed that the air had been absorbed and that the left chest was filled with fluid (blood) (Fig. 2).

On November 18, 1930, large amounts of dark-colored blood began to escape from the wound of entrance with an immediate improvement in the general condition of the patient. In twenty-four hours after the blood began to drain, the heart was back in its normal position and only a small amount of fluid remained in the chest (Fig. 3). Temperature, pulse and respirations returned to normal but the swelling and crepitation in the neck still remained.

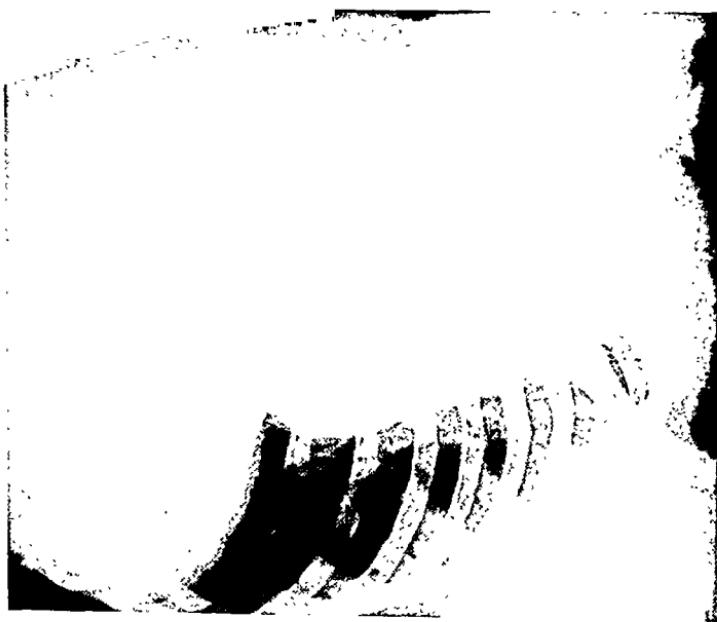
On the third day after the injury there were signs of residual fluid in the chest and an aspirating needle was inserted in the eighth interspace in the

FIG. 1.



Photograph of patient showing ecchymosis in neck and chest wall.

FIG. 2.



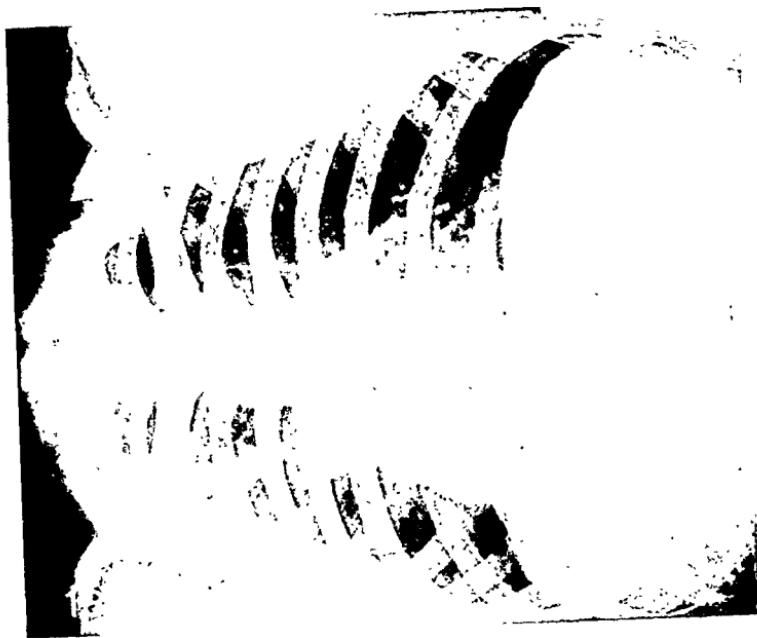
Roentgenogram showing displacement of heart by fluid and air in left pleural cavity.

FIG. 3.



Roentgenogram of chest after considerable blood had drained from entrance wound.

FIG. 4.



Roentgenogram showing expanded lung after removal of blood.

posterior axillary line and 750 cubic centimeters of dark unclotted blood removed. Further aspiration was not necessary. The lung expanded well and the breath sounds were clearly heard but were slightly distant (Fig. 4). The swelling in the neck subsided and the bullet could be easily felt under the left mandible.

COMMENT

The unusual course of the projectile in this case, with its manifold physical findings, demonstrates the extent of injury that the body can receive and still suffer little permanent disability. The course of the bullet is shown to have fractured the ninth rib, then ricocheted upward through the left lung to the clavicle and then to the angle of the left mandible.

On entrance to the hospital the first consideration is that of treating the initial shock. It has been found that unless the injury is to the heart, or one of the large vessels in the thorax, this can be overcome.

The next most important factor is that of immediately putting the patient at absolute rest. Morphine sulphate is given in doses sufficiently large to control respiration to within as near normal limits as possible. The routine is to administer $\frac{1}{4}$ grain of morphine sulphate every three or four hours as long as respiration is twenty per minute or above.

Wounds, such as this one, that do not suck air are left open and the blood will sometimes drain out of its own accord. However, aspiration of fluid blood must be done as soon as the bleeding has stopped. Early removal of the blood lessens the possibility of fibrin deposit on the pleura. The likelihood of empyema is also much less with early removal. At the end of forty-eight hours an aspiration is done at the lowest fluid level and is repeated as often as there is a reaccumulation.

Operation is advised in this type of case only when there is a bleeding from the chest wall. Under this plan of conservatism in the mortality rate in this clinic is 10 per cent. Empyema following penetrating wounds of the chest is less than 3 per cent.

I. TRAUMATIC CYST OF BRAIN. II. WANDERING BULLET IN BRAIN. III. INTRACRANIAL ARTERIOVENOUS ANEURYSM*

By J. CALVIN WEAVER, M.D.

Associate Professor of Surgery (Neuro-Surgical Division), Emory University
School of Medicine

TRAUMATIC CYST OF THE BRAIN

AS ANY operation on the brain is usually looked upon by the laity and the medical profession generally as a most formidable and melancholy procedure, both on account of the high mortality, and among those surviving a large percentage of only partial cures; a complete cure of a lesion requiring a major operation upon the head, particularly if located in the posterior fossae, is always a most gratifying experience.

Cysts of the brain, a rather rare entity, occasionally offers the opportunity for such a result.

Many works on neurology make no mention of cysts of the brain of traumatic origin, while a few dispense with the subject with a mere mention of the possible existence of such a condition.

One outstanding authority says, "the origin of traumatic cysts is not yet clearly explained. They occur chiefly in the mantle of the cerebrum and in the cerebellum. Their symptoms may be very similar to those of tumor.

"It is not yet proved whether a localized serous meningitis may give rise to the formation of cysts."¹

Under the heading "Remote Effects of Head Injury" Rawlings mentions arachnoid cysts as follows:

"Where the cysts—often of considerable size—is lined by a thin, shiny, membranous wall, the contained fluid is almost colorless, closely resembling cerebrospinal fluid, but albuminous and having no sugar-reduction reaction.

"The fluid is at high tension, spurting out when the cyst is punc-

* Report of Cases from the Surgical Department (Neuro-Surgical Division) of Emory University School of Medicine.

tured. The cyst usually lies in relation to the arachnoid membrane. Hence the name, 'arachnoid cysts.'

Such a cyst, whether the result of a hemorrhage which the tissues have attempted to wall off by a fibrous capsule, the corpuscles and blood pigment being eventually removed with a clear, serous fluid remaining, or whether it be a condition described by Krause as "Arachnitis chronica adhesiva circumscripita" if it should happen to be placed in a position calculated to block the circulation or current of cerebrospinal fluid, as, for instance, stopping the foramina of Luschka and Magendie, marked internal hydrocephalus will result with manifestations of a tumor in the mid-line of the posterior fossa with serious and destructive symptoms.

The following case of this nature is of interest on account of the severity of symptoms simulating a brain tumor and the perfect cure following operation. There was an extreme degree of internal hydrocephalus, as is well shown by roentgenograms.

The history of the case, with the outstanding symptoms, is as follows:

M. W., #34634, a laborer, aged 24, was referred to the neurological service of the Emory University division of Grady Hospital late in August, 1929. The records show that several months previously he was on the medical service, but decided to return home, and after growing worse, returned for further observation and was reentered on the medical service for further study.

In June 1929, Dr. W. A. Smith (neurologist) made the following notation:

"The neurological examination is essentially negative except for a tremor of both hands, and an abortive ankle clonus on both sides. No evidence at this time of localized brain lesion. I can not see any posterior clinoid process in the X-ray, and there may be some thinning of the floor."

Eleven days later Dr. K. Rice reported practically the same findings with the addition of slight edema of both discs. During my absence on vacation Doctor Rice injected the ventricles with air and found a marked internal hydrocephalus.

This patient was a young married negro. Four children were living and well. Family history negative for any neurological conditions. His health had always been good. Some eight or nine years ago he was struck on the head by a falling limb of a tree. Was badly dazed for a short time but did not quit work. His companion was killed at the same time by a blow from this limb. Two years previous to the beginning of his present illness, he was confined to his bed for more than two weeks with a severe attack of pneumonia. There is no history of any other injury.

Chief Complaints.—

1. Headaches.
2. Dizziness and staggering gait.

3. "Falling out" spells.
4. Vomiting.
5. Disturbance of vision.
6. Diplopia.

The onset of headaches began about a year ago, were mild at first and gradually but slowly grew worse. They were later attended with nausea and vomiting. When lying on back there was a sensation of fulness in his head described as "blood rushing to head." When arising after lying down he would go temporarily blind; everything would be dark. Has had several "falling out" spells.

Though there was no history of syphilis, during February and March of 1929 he was given four injections of neosalvarsan by his family physician who attributed his nervous symptoms to syphilis.

Neurological Examination.—

Cranial Nerves.—1. Sense of smell present right and left. 2. No nystagmus, vertical or horizontal. Pupils are dilated from homatropine two days previous. Visual fields normal. No diplopia now, but patient has noticed double vision several times. There is definite choking of both discs, two to three diopters, with small hemorrhage in both discs. 3, 4, 6. There is a suggestion of exophthalmos. No drooping of lids. All external movements of eyes are well performed. 5. Sensation in face present right and left. Motor fifth normal. Corneal reflex present right and left. 7. No facial paralysis. Can taste anterior two-thirds of tongue right and left. 8. Hearing present right and left, normal to watch tick. No history of otitis media. No tinnitus. Cf. history of numerous attacks of dizziness. 9. Gag reflex present. Does not choke on swallowing. Taste present posterior third of tongue right and left. 10. Has frequent vomiting spells. Pulse 80. Blood-pressure 130/70. 11, 12. Normal.

Cerebrum.—Frontal.—Patient is well orientated as to time, place and people. There is a coarse tremor of both hands. *Precentral.*—No history of convulsions of either local or general nature. No paralysis of any group of muscles. *Postcentral.*—Sensation present right and left, epicritic, protopathic and deep. No astereognosis. No adiakokinesia. Joint sense present right and left. Sense of position present. *Temporal.*—Patient is right-handed. No aphasia. No uncinate gyrus fits. *Occipital.*—Cf. history of blind attacks following sudden change of posture; possibly a type of visual Jacksonian attacks.

Cerebellum.—Definite Rhombergism. Patient has a staggering, reeling gait but does not fall to any particular side. With the "falling out" spells he claims to fall forward.

Reflexes.—Pupils widely dilated. Epigastric and abdominal present right and left. Cremasteric present right and left. Patella present right and left. Tendo Achillis present right and left. Babinski absent. *Serological.*—Blood and spinal fluid Wassermann negative. *X-Ray.—Skull.*—"Sella definitely enlarged. Posterior clinoid process indistinct. No evidence of any intracranial pressure." *X-ray—following air injection into ventricles—Skull.*—Examination of the ventricles after removal of fluid and injection of air shows no asymmetry. Ventricles unusually large indicating an increased amount of fluid producing an internal hydrocephalus. Several calcified areas lying just below the mid-ventricular region.

Impression.—Considering the objective findings, coarse tremor of both hands, reeling gait, bilateral choked discs, marked internal hydrocephalus as shown by roentgenograms in association with the subjective findings of history of headaches over a long period, dizziness, blind attacks, diplopia, tendency to fall forward preceding "falling out" spells, there is reason to believe the patient has a mid-line lesion in the posterior fossa.

Operation.—The orthodox cross-bow incision, with mid-cervical incision to spine was used to expose the suboccipital region. The cerebellum was exposed and on opening the dura a large arachnoid cyst was found bulging from between the cerebellar lobes. It was covered by a thin membrane, through which the contents of clear, thin fluid could be seen. The cyst was opened, the roof was trimmed off with scissors, the dura left open and the operative field closed layer by layer with interrupted sutures of black silk. (Frontispiece, Fig. 1 and Fig. 2.)

Postoperative.—Patient made a rapid and complete recovery. A year following operation patient has gained weight, is working every day and appears to be perfectly well in every way.

REFERENCE

¹OPPENHEIM, BRUCE: Text-Book on Nervous Diseases, Translation, Vol. 11, p. 889.

WANDERING BULLET IN BRAIN

Though in civil practice the opportunity of observing bullet wounds of the brain comes rather infrequently, at the same time there comes a sufficient number of "occasional cases" to lend interest to this type, particularly if certain important centers are involved. The number of such cases during the late war furnished ample material for information tending toward a general improvement in the handling of this type of cases.

It is generally understood that despite the damage from fragments of bone, hemorrhage, indrawn tufts of hair, the most important feature to be reckoned with, is infection.

Fortunately some retained missiles become encapsulated, the patient recovers and continues without symptoms. It probably is true that the heat of the bullet may cause it to be sterile, and in a patient with high resistance, no serious infection develops, such as meningitis or encephalitis. In the event the patient escapes such infection, functional symptoms may result from a wandering bullet which at first may have stopped in a silent area, only later to find its way through weight of the bullet gravitating through the soft brain tissue to its final destination.

The symptoms resulting depend entirely upon the locations it traverses and the area in which it finally stops.

Krause¹ reports an interesting case as follows:

September 2, 1909, a young man was shot with revolver, 6 mm. caliber, the bullet entering close below the frontal eminence. There was immediate paralysis of the left half of body. Six days later the bullet was located in the posterior upper portion of the skull in the region of the upper parietal lobe. The track of the gunshot wound ran sagittally and somewhat posteriorly and upward through the right hemisphere. Patient left his bed after the eleventh week, the paralysis gradually improving.

An X-ray examination made January 28, 1910, showed that the bullet had returned to the region of its entrance to the front, and that it lay in the roof of the orbit a few centimeters from the frontal bone. The patient was able to walk without a crutch or stick, only a slight residual spasticity in left leg being left.

The wandering of the bullet back to the region of the point of entrance caused no symptoms except brief periods of headache, such as he experienced when first shot.

As to the management of bullet wound of the head—and what applies to bullet wound is particularly true of "ice pick" wounds of the skull—neurological surgeons are in complete accord that immediate operative interference should be instituted and débridement of the tract be done. After contused brain and foreign substances have been removed, the dura is closed and a small rubber wick drain placed down to the dura.

The following case is of interest from two points of view, *viz.*, the late focal symptoms created by the wandering of the bullet, and the great improvement of patient after the bullet was removed.

W. C., aged 42, a negro bricklayer, was admitted July 5, 1930, to surgical service (neuro-surgical division) of the Emory University School of Medicine, Grady Hospital.

He had sustained a gunshot wound of the upper left occipital region the day previous while on a fishing trip. He was knocked unconscious when struck by the bullet but later improved and was admitted to the hospital in very good general condition. He could not be operated on immediately as the X-ray department and the operating room had just been destroyed by fire.

The initial wound was carefully disinfected and dressed and healed with practically no infection. Several days later, as he seemed to be doing nicely, and on account of the temporarily demoralized condition of the hospital, he was allowed to return home with instructions to report later for observation.

On August 22, 1930, he was readmitted with the following notation: "Was discharged latter part of July following gunshot wound of head greatly improved. Has been suffering from frontal and occipital headaches of gradually increasing severity since discharge. They are much worse at night.

"Patient is awkward—unable to use hands and feet as formerly, walks with uncertainty and can not perform finer movements.

"Patient has some difficulty of speech and can not choose words well. There is a definite right hemianopsia to rough test. External movements of eyes well performed.

"Patient has a lethargic appearance. All tendon reflexes increased.

"There is a definite unsteadiness of gait."

On August 26, 1930, visual fields were tested by Dr. A. V. Hallum and showed definitely an interference of sight to the right, also the right lower quadrant. See Fig. 1.

Vision	O D =	20 +	No scotoma
		200	
O S =	20 +		
		200	

Neurological Examination.—Cranial Nerves.—1. Patient can smell right and left. 2. Eyes are parallel; pupils equal. There is no nystagmus, vertical nor horizontal. Ophthalmoscope shows the left eye disc clear cut, there is no swelling nor choking. Vessels are normal size. The right eye shows similar findings. There is no choking nor swelling of the disc. Visual fields show a right-sided hemianopsia, and there is also an interference with vision. 3, 4, 6. All external movements of the eye well performed. Palpebral margins are normal distance apart. 5. Motor and sensory fifth both seem normal. Sensation present and equal right and left. Corneal reflex present right and left. 7. Voluntary and emotional movements well performed. Patient shows mask-like countenance resembling the Parkinsonian expression. Also a certain amount of dysarthria is present. Taste is present anterior two-thirds of tongue right and left. 8. No history of tinnitus. No otitis media. 9. Gag reflex present. 10. Pulse 86. 11. Normal. 12. Normal.

Cerebrum.—Frontal Lobe.—Patient is well orientated as to time, place and people. No tremor of outstretched fingers. *Precentral.*—No paralysis of any group of muscles. No history of convulsions, either general or localized. *Postcentral.*—Sensation to touch present and equal right and left. No astereognosis. Joint sense present and equal right and left. *Temporal Lobe.*—No convulsions. Patient is right-handed. No uncinate gyrus attacks. *Occipital Lobe.*—Shows symptoms of a right homonymous hemianopsia with blindness in the lower fields right to rough test.

Cerebellum.—No nystagmus. Finger-to-nose test well performed right; not so good left. No adiadiokinesia. After patient stands a few moments he develops some Rhombergism. There is some unsteadiness in patient's walk but he does not reel to either side nor fall backward nor forward.

Reflexes.—Deep arm reflex present and equal right and left. Abdominal and epigastric equal right and left. Babinski absent right and left. Patellar active right and left.

Impression.—With the gunshot wound in the occipital region near the midline, and the X-ray showing a large bullet which has gravitated some 6 centimeters downward to the occipital protuberance, with a right hemianopsia

present, and a quadrantanopsia of both lower quadrants present, there is evidently either a cyst, or possibly an abscess, in the visuosensory area of the occipital lobe above the calcarine fissure.

Recommendation.—It is recommended that a trephine be done over this region, and the bullet be removed if possible, and a drainage of either the cyst or abscess.

Operation.—On August 27, 1930, under local anesthesia, a vertical incision was made slightly to the left of the mid-line, the lower end of incision being on a level with the occipital protuberance. The skull was trephined and the dura opened about 3 centimeters above the lateral sinus. At about the depth of 1 centimeter in the brain toward the mid-line, the bullet was located and removed. There was a small accumulation of bloody fluid, some necrotic brain tissue, and a few hairs caught in the flattened, distorted bullet of large caliber. The incision was closed without drainage. (Figs. 3, 4, and 5.)

The headaches rapidly cleared up. In forty-eight hours the visual field had shown great improvement.

On September 6, 1930, the field was perceptibly enlarged. (See Fig. 2.) One month later the patient was seen and showed remarkable improvement in every way, though right lower quadrants had not cleared up to rough test.

As the visual field disturbances were caused by a gradual gravitation of the bullet into these visual centers, there is reason to hope that the visual disturbances will show still further improvement.

REFERENCE

¹ Krause: "Surgery of Brain," vol. 111, p. 941.

INTRACRANIAL ARTERIOVENOUS ANEURYSM

Though Harkness¹ about a year ago collected some 621 cases of arteriovenous fistulae of the intracranial type, the long period of time covered by this series of cases makes the condition a rather rare one; so rare that many surgeons go through years of practice without seeing one case.

As he appropriately says, "a malady of such rarity, and with such striking symptomatology is deserving of record wherever encountered."

Even Matas, who has had at least as much experience as any living American surgeon with this type of cases, reports only forty cases of arteriovenous fistulae of different types, only nine of this number being intracranial. In his series of cases the longest time that elapsed between the injury and the diagnosis of arteriovenous injury as such was eight years.

He brings to notice the fact that the typical regional and local signs of arteriovenous fistula (thrill, pulsation, etc.) may exist even

FIG. 2.



FIG. 3.



Case M. W.—Traumatic cyst of brain. Air injection of ventricles. Internal hydrocephalus.

Case W. C.—Wandering bullet in brain. Location of bullet on admission to hospital. No. 1.

FIG. 4.



FIG. 5.

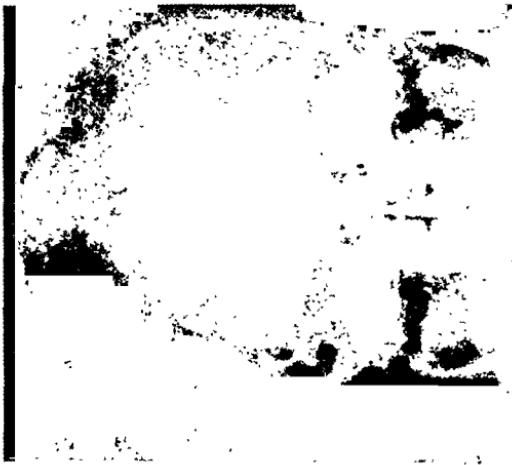
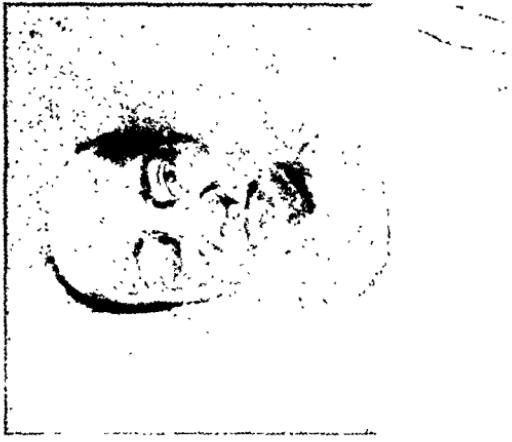


FIG. 6.



CASE W. C.—No. 3.—Wandering bullet in brain. Bullet gravitated to occipital protuberance. No. 2. later.

CASE W. C.—No. 3.—Wandering bullet in brain. Showing bullet on left side.

CASE C. M.—Intracranial arteriovenous aneurysm. Proptosis of right eye.

FIG. 7.



CASE C. M.—No. 1.—Lateral view intracranial arteriovenous aneurysm. Bullet in left orbit. Small particles lead in right fossa, causing aneurysm eighteen years later.

FIG. 8.



CASE C. M.—No. 2.—Front view. Intracranial arteriovenous aneurysm. Bullet in left orbit. Gunshot wound eighteen years ago.

to a very notable degree, but unless they are associated with large, pulsating veins and marked varicosities (showing that the fistula is large and allows a stream of arterial blood to go through with sufficient force to overcome the resistance of the valves), they do not, as a rule, affect the heart or general circulation.

This is well shown in the intracranial arteriovenous fistulae typified in traumatic pulsating exophthalmos caused by the rupture of the internal carotid into the cavernous sinus. In this form of arteriovenous communication the auscultatory signs and thrill are loudly and widely diffused through head and neck, but are not followed, even after years of existence, by notable cardiovascular disturbances.²

The case to be reported from the Neurological Service of the Emory University School of Medicine is of general interest on account of the rarity of this type of case, and of particular interest on account of the long period of time that elapsed between the injury and the diagnosis of the arteriovenous injury, this case going eighteen years before developing symptoms that led to a final diagnosis.

In keeping with Matas' experience and finding, there were no cardiac symptoms resulting from this condition.

At the request of Doctor McDougal, who had made an exploratory operation of the right orbit, a neurological examination was made with the diagnosis of intracranial arteriovenous aneurysm.

Neurological Examination (August 16, 1930).—

Patient is a medium-sized mulatto male adult, lying quietly in bed. He does not seem to be profoundly ill. There is exophthalmos of the right eye, with marked edema and ecchymosis of the upper lid, which probably has resulted from the incision at a recent operation through the right eyebrow.

Cranial Nerves.—1. Patient can smell right and left. 2. Eyes are parallel. The pupil in the right eye is rather dilated, probably on account of the homatropine. The left pupil reacts to light and accommodation. There is no visual defect to rough test in the left eye. Right eye also shows similar findings to rough test. Ophthalmoscope shows an engorgement of the veins of the right disc but no definite swelling nor choking. Left eye shows definite atrophy, though the veins are rather small. Vision: O D = 20/50; O S = 20/70. 3, 4, 6. All external movements of the eye well performed. There is no nystagmus. There is marked exophthalmos in the right eye. Palpebral margin of the left eye normal. 5. Sensation to touch present and equal right and left. Motor fifth normal. Corneal reflex left is very active. 7. Voluntary and emotional movements well performed right and left. Taste present anterior two-thirds of tongue right and left. 8. There is a history of ringing in

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the left ear, which developed during the convalescence after the gunshot wound and has continued ever since. Patient cannot hear watch tick with the watch against the left ear. Can hear watch tick about 10 inches from right ear. 9. Can taste posterior third of tongue right and left. Gag reflex is present. 10. Pulse 72. Blood-pressure 112/78. No vomiting. 11. Normal. 12. Normal.

Cerebrum.—*Frontal Lobe.*—Patient is well orientated as to time, place and people. There is no fine tremor of outstretched fingers. *Precentral.*—There is no paralysis of any group of muscles. There is no history of either Jacksonian or generalized convulsions. Sensation is present and equal right and left. No numbness in any part of the body. *Temporal Lobe.*—No uncinate gyrus attacks. Patient can repeat any sentence given him. There is no evidence of aphasia. There is no marked thirst or appetite. No change in disposition. *Postcentral.*—Sensation is present and equal right and left. No astereognosis. Joint sense present and equal right and left.

Cerebellum.—Finger-to-nose test well performed right and left. Heel-to-knee test well performed right and left. No nystagmus. He states that he has a dizziness quite often and does have some unsteadiness in his gait while walking, but does not reel in the same direction every time.

Reflexes.—Deep arm reflexes present right and left. Patellar normal right and left. Achilles tendon present and equal right and left. Babinski absent right and left. Abdominal and epigastric present and active right and left. Cremasteric active right and left.

Sphincters.—Control normal. No rhombergism. Stethoscope reveals a definite bruit which is constant, but accentuated with the systolic sound and heard particularly over the mid-line of the forehead. There is a definite amount of pulsation of the exophthalmos though it is not extremely marked.

Impression.—Arteriovenous sinus, probably of the internal carotid and cavernous sinus, resulting from the gunshot wound some eighteen years ago.

It was decided that ligation of the right internal carotid be done, which was accomplished under local anesthesia by Doctor McDougal. With the artery exposed, the bruit was obliterated several times by pressure on the artery, only to return immediately on release of pressure. In forty-eight hours the exophthalmos had receded over 50 per cent., while the bruit could no longer be heard. (Figs. 6-8.)

The patient did nicely for several days but unfortunately developed a periurethral abscess, with high fever, went into a uremic coma and passed out before a second photograph showing marked improvement in the eye condition could be made. His death could in no wise be connected with the intracranial lesion.

REFERENCES

- ¹ HARKNESS, G. F.: "Intracranial Arterio-Venous Aneurysm. Pulsating Exophthalmos," *International Journal of Medicine and Surgery*, vol. 43, No. 5.
- ² MATAS, RUDOLPH: "On the Systemic or Cardiovascular Effects of Arteriovenous Fistulae." *Transactions of The Southern Surgical Association*, vol. 32, 1923.

SURGICAL DISEASES AND INJURIES OF THE BLOOD-VESSELS

A Clinical Study of Fifty-five Cases*

By J. L. CAMPBELL, M.D., F.A.C.S.
Atlanta, Georgia

ENTERING the operating room of the Atlanta Medical College, June 7, 1898, I saw that one of my colleagues had opened a large aneurysm of the femoral artery under the impression that it was a "bubo." This tragedy so impressed me that I began to study the subject and I am now, after thirty-two years, more and more convinced of the truth of the statement quoted by Matas that "there is probably no other disease which exhibits such a long list of celebrated diagnostic errors." Prior to October, 1926, 25 per cent. of all the aneurysms which came under our observation at the college clinic and Grady Hospital had been opened under the impression that they were abscesses.

Arterial aneurysms were identified by Galen during the second century A.D. Acute traumatic aneurysms were described by Aetius as "pulsating hematomas" in the sixth century. After a lapse of 1200 years William Hunter recognized an arteriovenous aneurysm at the bend of the elbow. About the same time his illustrious brother, John, proved that conservation of the collateral circulation was the chief factor in the treatment of blood-vessel lesions.

Matas and others have thoroughly described the fundamental principles of aneurysm formation, pathology, etc. It is not, therefore, my purpose to review their work, but to present a series of fifty-five cases which have come under our observation since 1898. All of them were in peripheral or surgically accessible vessels. Nine of these cases were seen in the college clinic and Grady Hospital prior to October, 1921. Forty-four represent the aneurysms (exclusive of the aortic) among a total of 42,635 admissions to the Emory University division of Grady Hospital since its organiza-

* From the Department of Clinical Surgery, Emory University.

tion in 1921, and one white man seen by Dr. W. P. Nicolson and myself at the Steiner Ward of Grady Hospital.

In the entire group of fifty-five cases the vessels were involved as follows:

Artery	Times	Idiopathic	Traumatic		
			Arterial	Arteriovenous	Total
Femoral.....	17	8	4	5	9
Popliteal.....	12	10	1	1	2
Carotids.....	8	5		3	3
Brachial.....	3		3		3
Digital.....	3		3		3
Subclavian.....	3	1		2	2
Profunda femoris.....	2			2	2
Temporal.....	2		2		2
Anterior tibial.....	1		1		1
Posterior tibial.....	1	1			
Radial.....	1		1		1
Dorsalis pedis.....	1		1		1
Pulsating exophthalmos.	1			1	1
Total.....	55	25	16	14	30

The ages of these patients varied from nineteen to fifty-six years. There were five women, in whom the following vessels were involved: the popliteals twice, carotid once, posterior tibial once, and radial once. All were idiopathic, except the radial, which was due to a contusion.

Following the classification suggested by Matas, our cases may be grouped:

1. *Sacculated*.—Where only one opening connecting the artery with the sac could be demonstrated. The cases in this group were not all idiopathic, for one of six months' duration—resulting from a bullet wound—had a well-formed sac connected with the artery by a single elliptical opening.

2. *Fusiform*.—Where the proximal and distal openings had become separated, even though there was a definite groove along the original course of the artery.

3. *Pulsating Hematomas*.—Where the patient was seen before

a well-defined sac had developed, but after the thrill and bruit had become established. The sac-building period differs widely; but in one case, the result of a stab wound, the cavity in the clot was lined, within thirty-two days, by frail tendrils of connective tissue along which the intima was beginning to climb.

4. *Arteriovenous Aneurysms.*—Where there was either a direct fistula or an indirect communication through a pulsating hematoma or sac. In this group we have placed the one pulsating exophthalmos.

Twenty-five cases—45.4 per cent. of the entire series—were idiopathic. It was impossible to trace the incidence of syphilis in these patients because many of them who gave a negative Wassermann were found to have been given "shots for bad blood," either by a private doctor or in the clinic. Ten—40 per cent. of the idiopathic cases—were located in the popliteal artery. Eight—32 per cent.—were in the femoral; and five—20 per cent.—were in the carotids. The posterior tibial was affected once, due to spontaneous rupture which occurred as the patient was getting out of bed. There was one subclavian, located in the second portion of the artery. It was small, but had given a great deal of pain and the patient had been treated for rheumatism. Ten years after I operated on this case the patient died in Grady Hospital from a ruptured aneurysm of the first portion of the aorta.

As usual, the largest ratio of idiopathic aneurysms was found in the popliteal artery. Four of them had ruptured before admission and blood, varying in amount from 500 to 2,000 cubic centimeters, was extravasated into the popliteal space. One of these patients had attempted to open the mass at the back of his knee, using the negro's favorite instrument—a razor. He had succeeded in getting it to bleed freely; then his courage had failed and he had come to the emergency clinic. He was admitted to the hospital. At operation a tourniquet was placed around the thigh and an incision made into the mass, which contained 2,000 cubic centimeters of liquid and clotted blood. The openings in the artery were sutured with No. 1 chromic catgut and the cavity packed with vaseline gauze. The sides of the sac and the walls of the cavity caused by the extravasated blood were granulating nicely when he suddenly had a secondary hemorrhage and died a few hours later, despite transfusion and other restorative methods.

We have found it very difficult to get union in these sclerotic vessel walls, especially where the patient has syphilis; so I have adopted the plan of curetting the margins of the openings and an adjoining area of the sac before suturing them.

In one of the popliteal group, there was a spontaneous cure. The sac which had pulsated on admission filled with a firm clot and, when incised, the opening in the artery had healed. The patient made an uninterrupted recovery. In another, the patient had complained of pain in the leg and knee for the past six or eight months. Eighteen months before admission to the hospital he had stuck a nail in his foot, for which he had received tetanus antitoxin. The doctor who treated him at that time found he had a chancre and gave him several doses of some intravenous antiluetic treatment. Later, when the knee and leg began to give pain the negro came to the clinic and was given still further antileutic treatment—a diagnosis of arteriosclerosis and possibly syphilitic osteomyelitis being made, although no positive bone changes were demonstrated with X-ray. Early in July, 1930, he came to the emergency clinic late one night complaining of tingling and severe pain in the leg and foot. At this time the aneurysm was discovered and he was advised to go into the hospital, but refused. Two days later he returned with beginning gangrene of the foot, which gradually extended up the leg to near the middle. When admitted the thrill had disappeared and the bruit was very faintly heard. It also disappeared in twenty-four hours. The pain was severe, at times requiring morphine. When palliative treatment failed to arrest the gangrene, the femoral vein was ligated in the upper third of the thigh and the aneurysm incised. The sac and artery proximal and distal to it were filled with a firm clot which was evacuated, but this was not followed by bleeding. The openings were closed and the sac packed with vaseline gauze. The gangrene receded some, but finally a definite line of demarcation formed and the leg was amputated about 12 centimeters below the knee. He then made a rapid recovery.

There was nothing unusual in the eight idiopathic femoral aneurysms, except that three of them occurred in one patient. Another patient, sent in with a diagnosis of fascial sarcoma, had a ruptured aneurysm in Hunter's canal. The history of a pulsating tumor, gradually increasing in size and (at the time of admission)

characterized by a bruit over one area of the mass, made us suspect a ruptured aneurysm. This proved to be the case. It was cured by suturing the arterial openings within the sac and packing the cavity with vaseline gauze.

One of the five aneurysms of the carotid occurred in the same patient who had previously had three in the femoral artery. Another was in a woman who had advanced pellagra. The aneurysm had given no pain, though she had noticed it for several months. Until it ruptured she paid no attention to it. Then she went to the clinic complaining of difficult breathing, pain, bloody expectoration, and inability to swallow. The out-resident intern was just ready to open it within the throat, thinking that it was a peritonsilar abscess, when the surgical resident recognized it as a ruptured aneurysm. Incomplete occlusion failed to produce clotting. Later the artery was ligated in two places, but still the blood in the sac did not clot and she refused further treatment.

There were thirty traumatic aneurysms in this series. Twenty—66.6 per cent.—were due to gunshot wounds, of which thirteen were arteriovenous. Six—20 per cent.—were caused by contusions: two in the temporal and two in the digital arteries; one in the lower end of the radial where it winds around the radius; and one in the dorsalis pedis artery. It will be noted that these vessels all lie close to the bone, and the blows which apparently caused the aneurysms ruptured the artery. Three—10 per cent.—were due to stab wounds; one in the digital artery of the thumb to a splinter, the two in the brachial to a knife stab; the pulsating exophthalmos, to a fracture of the base of the skull.

Among the twenty gunshot wounds, the femoral vessels were injured nine times: four resulting in arteriovenous aneurysms and three in pulsating hematomas, in one of which both the artery and vein were involved. The remaining two were in Hunter's canal and followed gunshot wounds inflicted nine and two years before admission. In the former, the aneurysm had been present three years; the heart was enlarged and decompensated to a marked degree. Owing to the violent thrill and bruit present, he was sent to surgery with a diagnosis of an arteriovenous aneurysm, but Branham's sign was not present. Under local anesthetic the sartorius muscle was reflected laterally and a cone-shaped sac 9 centimeters long by 3

centimeters in diameter was exposed. A rubber tube was clamped around the artery just proximal to the sac, which was opened its entire length. There was a diverticulum, 2.5 centimeters deep and 1.5 centimeter in diameter, extending posteriorly into the intermuscular septum. Its floor and walls were lined with calcareous flakes, while the walls of the aneurysm were thin and smooth. A double ligature of No. 1 chromic catgut was placed around the artery at the site of the rubber tube, the proximal opening sutured from within the sac, and the cavity packed with iodoform gauze. (This was previous to using vaseline gauze.) Owing to the presence of the calcareous deposits in the diverticulum, this wound was a long time in healing. The heart condition was not affected by the operation, as occurs in arteriovenous aneurysms, but the patient was benefited by the long rest in bed.

In the other case we did a Matas restorative aneurysmorrhaphy, but two weeks later the wound broke down and the patient had a severe hemorrhage, but recovered. When last heard from he was doing his usual work.

Three gunshot wounds of the femoral just below the profunda (one included the artery and vein) resulted in gangrene of the leg and thigh, necessitating amputation about 8 inches below the wound. In one of these, an arterial anastomosis was done, but the trauma was so great that the circulation was never established and an aneurysm developed at the site of the wound about three months later. It was cured by ligation of the external iliac. In the other two, a thrill and bruit were detected about ten days after the amputation (three weeks after the wound). Both of these were cured by opening the hematoma and ligating and suturing the wound in the vessels.

There were five arteriovenous aneurysms of the femoral vessels. They were all caused by gunshot wounds fired at various ranges. Three of them were recent and of no special interest. The other two were in the upper end of the artery and were of long standing. One of these was operated on at the college clinic prior to 1921. The patient was in bad condition. The vessels, especially the vein, were widely dilated, the walls thin and friable. During the operation the patient lost a large quantity of blood and died shortly after it was completed. Profiting by our past experience, we kept our

next case in bed for two weeks in order that he might regain as much of his lost heart compensation as possible. At operation the vessels were exposed by an incision about 12 centimeters long, beginning about 2 centimeters above the inguinal ligament and extending down the course of the vessel to well below the aneurysm. The lower end of the iliac artery measured about 2 centimeters and the vein about 3 centimeters in diameter. Their walls were thick and fibrous. The artery continued about the same size for 2 centimeters below the origin of the profunda, while the vein was widely dilated for at least 4 centimeters lower, where the dilatation ended abruptly as if a fibrous band were drawn around it. There were a large number of tributary vessels which required ligating as the exposure continued. The profunda artery and vein were also ligated. When the field was well exposed rubber tubes were clamped tightly around the artery and vein above and below the fistula. There was such an extensive fusion between the vessels that an attempt was made to do a closure from within the vein. Because of the condition of the vessel walls, a plexus of vessels entering from behind, and the size of the fistula, this proved impossible. Therefore, a quadruple ligation was done and the lumen of the vessels between the ligatures obliterated by a double row of chromic catgut sutures. The wound was closed without drainage and the patient made an uneventful recovery.

During his preoperative period of rest and postoperative convalescence, Dr. Carter Smith, medical resident in the University division of Grady Hospital, demonstrated by a careful study that a great increase in the efficiency of the circulation resulted from operative closure of the fistula.*

The remaining arteriovenous aneurysms were located: three in the common carotid and internal jugular vein (two negroes and one white man); two in the subclavian; one in the popliteal. The latter was not recognized because of extravasated blood and a low-grade cellulitis until the cavity was opened. In the profunda femoris there were also two which were mistaken for femoral aneurysms. In one of these the thrill and bruit cleared up when the profunda was ligated

* Doctor Smith's paper, "A Study of the Circulation in a Patient with an Arteriovenous Aneurysm before and after Operation," is to be published in the *Archives of Internal Medicine* in the near future.

proximal to the wound, but recurred a short time later. The remaining one was cured by proximal and distal ligation. One of the subclavian cases left without operation.

The pulsating exophthalmos was cured by partial occlusion of the internal carotid artery with a fascial band. The thrill and bruit which so annoyed the patient disappeared as soon as the fascia was drawn around the artery and had not returned when he was last seen—about two months after the operation.

Six of our thirty traumatic aneurysms were due to contusions of various types. They were in the small arteries where collateral circulation was abundant, and were cured by proximal and distal ligation with extirpation of the sac.

It is not possible in this article for me to give to the two brachial aneurysms, or pulsating hematomas, the space they deserve. In both patients definite aneurysmal symptoms developed in about fourteen days after the injuries made by a knife stab entering at the posterior margin of the deltoid muscle. Both cases were seen in the clinic a few hours after injury. No indication of an arterial wound was observed at that time or for several days. Nothing indicated nerve injury; yet, two weeks later there were definite nerve symptoms in the arm, forearm, and hand, and a well-marked thrill and bruit over the mass which had formed just above the insertion of the deltoid. At operation no nerve lesion could be found, but when the clot and newly formed sac were removed an elliptical opening about 8 by 2 millimeters was found and sutured in both cases. The one seen five years ago is now firing the furnace at the Veterans' Hospital in Tuskegee, Alabama, while the one who has just left the hospital is recovering. These cases deserve more extensive study and will be reported at a later date.

It would seem that the diagnosis of aneurysm would be a simple matter when we consider the location of a tumor over an artery with pulsation, thrill and bruit. Yet, such is not the case. Almost anything is thought of before aneurysm, perhaps because of its rarity. Those sent in to us came with various impressions: abscess, fascial sarcoma, rheumatism, neuritis, osteomyelitis. In arteriovenous aneurysms the thrill and bruit are so pronounced that, when added to Branham's sign (slowing of the pulse when the fistula is closed, or the artery just proximal is occluded), failure in diagnosis

is almost impossible. In eleven of our cases the reduction in the pulse rate was from 18 to 20 per cent. The blood-pressure changes were not so constant.

The treatment of an aneurysm, whether recent or of long standing, often presents a serious problem. The collateral circulation must be preserved or more harm than good is done. The Matas operation—that is, procedure from within the sac—opened up a new era in this field of surgery and added many successes to the hitherto unsuccessful operations. To accomplish this the aneurysm must be so located that the proximal artery can be temporarily occluded. Therefore, it is best suited for the arms and legs. The subclavians are so well supplied with collateral branches that proximal occlusion alone does not give a dry field. The same is true of the carotids and of the femoral above the profunda. Although, in general, the Matas operation is the most trustworthy method, we had two failures because the sutured sac did not unite. Therefore, in our recent cases, I have curetted the margins of the arterial openings and a narrow area of the sac immediately adjacent to them before suturing. Then, instead of closing the sac, I have used one or two mattress sutures to narrow, but not close, the cavity which I then packed (firmly but not tightly) with vaseline gauze, allowing the wound to heal by granulation. Where the discharge has cleared up and granulation has become well established, narrow strips of adhesive are used to draw the wound together and secure a good closure.

In select cases—sacculated or fusiform aneurysms of the carotids, the iliacs, upper end of the femorals, or in any case where arteriosclerotic changes are extensive—the method which I have developed of partial occlusion with bands of fascia has given exceptionally good results. After exposing the artery as close to the sac as is practicable, I select a strip of strong fascia 1 centimeter wide and long enough to encircle the vessel twice. This is passed around and held flat against the vessel which has been cleared of its sheath. The stitches are so located that sufficient pressure on the artery can be secured to stop the pulsation, thrill and bruit, but not completely check the flow of blood. In the middle of the strip I take a mattress suture of medium-sized silk, and approximate the edges with two lateral stitches with the same material. The long end is then carried around the vessel and sutured. This method is a modification of

the Anel operation and an evolution of the work done by Halsted and Matas with metallic bands, tapes, *etc.* A good exposure is absolutely essential, because a wide area is necessary in order to get the fascia around the artery without wrinkling, and to preserve any anastomotic branches which might appear in the operative field.

SUMMARY

During the nine years since the organization of the Emory University division of Grady Hospital forty-four aneurysms—a ratio of 1 to 969 admissions—have been treated. Fifty-four and five-tenths per cent. were traumatic. Some were of long standing, but the majority developed in the hospital during convalescence from the wound which produced them. These we have classed as pulsating hematomas.

In two negroes and one white man definite symptoms of arterio-venous fistula formations were noted within ten days after gunshot wounds of the neck involving the common carotids and, while the time is not definitely stated, they developed quite early in other vessels affected. If operation is done as soon as the inflammatory process has cleared up, the continuity of the vessels can be restored unless too much of their lumen has been destroyed; then, a quadruple ligation can be done. In cases of long standing, where venous dilatation and numerous tributaries in the vicinity of the fistula are present, quadruple ligation with resection of the intervening segment is the operation of choice.

The size of the fistula seems to bear a definite relation to the dilatation of the veins and the effect on the general circulation. Branham's sign was noted within eight days in one case and quite early in the others which developed in the hospital. Temporary closure of the fistula reduced the pulse rate 18 to 20 per cent. in all cases, but a normal pulse rate and blood-pressure returned in a few hours, and the patients experienced no permanent discomfort from operations.

Partial occlusion with fascial bands has resulted in a permanent cure in six cases: four carotids and two femorals. The pain in the leg distal to the aneurysm was relieved within twenty-four hours after operation in both femoral cases. In the pulsating exophthalmos the bruit, or tinnitus aurium, was relieved at once

and had not returned when we last saw the patient—several months after operation.

The Matas operation—procedure from within the sac—has resulted in a cure of all but one of the ruptured aneurysms and pulsating hematomas in which it was used. In one femoral aneurysm, where a restorative operation was done, the wound broke down and the artery had to be obliterated and the sac packed. I have lately been curetting around the arterial opening before suturing, then packing the sac with vaseline gauze instead of attempting to close it as recommended by Matas. This may delay the convalescence for a while, but is beneficial as most of these patients need the rest. In our earlier cases we used a proximal and distal ligation, opened the sac, and packed it with iodoform gauze; but this method has now been abandoned.

There have been six deaths. One was from a mistaken diagnosis, whereby a femoral aneurysm was opened under the impression that it was a "bubo." Two of the arteriovenous aneurysms died of shock and loss of blood; one popliteal from secondary hemorrhage; and two of the femorals in Hunter's canal—one because of acute anemia on account of loss of blood when the aneurysm was opened by a private physician; the other from shock.

In one popliteal, gangrene of the foot and leg was present when the patient was admitted. Removal of the embolic clot did not relieve it and amputation below the knee was necessary. In another popliteal there was spontaneous cure. Gangrene of the forearm followed proximal and distal ligation of the idiopathic subclavian and necessitated amputation of the forearm just below the elbow. One case of carotid aneurysm was not completely cured, probably because the patient had pellagra and refused continued treatment.

Seven were discharged as improved. Of those in this group whom we have been able to follow, two are now well and all except one have been able to resume their occupation.

Three were not treated. Two of these signed a release and left voluntarily; one was sent out on account of the fire which occurred during June, 1930.

Thirty-nine—71 per cent.—were discharged as cured. If any of these have had a recurrence or further trouble, we have been unable to trace them.

EMPYEMA NECESSITATIS¹ (Unusual Sinus Tract)

By JAMES J. CLARK, M.D.
Atlanta, Georgia.

ON SEPTEMBER 1, 1930, C. T., colored male, aged 35 years, presented at the Emory University Colored Grady Clinic. His complaint was pain and aching in the upper right thigh. Examination revealed a hard, brawny swelling, which was extremely tender and inflamed. He stated that the preceding year the same condition had appeared and was treated with liniment and had cleared up. He thought it was rheumatism. He was directed to apply hot applications to his thigh, in an effort to aid the abscess in pointing. This was done at home. On his return to the clinic the following week, as it had not pointed, it was incised and drained. Relief was obtained for about one week, when he again complained of marked pain, the incision was reopened and more pus obtained.

On October 1 he was referred to the orthopedic clinic. The inflammation in the thigh had increased, he had lost weight and had become progressively weaker. He was unable to walk except with great difficulty and pain. A tentative diagnosis of osteomyelitis was made and he was admitted to Grady Hospital, Colored Division, on October 6, 1930.

History in Brief.—Family history essentially negative. Past history.—Born and raised in Georgia. Usual childhood diseases. Had pneumonia in 1928. Also jaundice. Gonorrhea in 1912. No history of other diseases such as typhoid, syphilis, malaria or tuberculosis. No shortness of breath, cough or hemoptysis. No edema. No pain in chest, night sweats or cardiac symptoms. Has worked steadily the past two years since his attack of pneumonia. No gastro-intestinal disturbances. No urinary tract disturbances, except cloudy urine since beginning of this illness. Neuromuscular essentially negative. Weight, best 150-155 lbs. Thinks he has lost some lately.

Physical Examination.—Patient is a well-developed negro male, lying quietly in bed, with right lower extremity flexed. In no evident pain unless moved, when right hip and thigh seems painful. Rational and coöperative. Head, ears, nose, mouth and throat negative. Chest.—Right chest less rounded than left. Does not expand well. Heart.—The apex appears to be in the fourth left interspace, about 10 centimeters from the mid-sternal line, but this cannot be accurately determined, as the heart action may be discerned over the entire precordium. Left border dulness 12 centimeters from mid-sternal line. Right border dulness indefinite but about one centimeter from mid-sternal line. There is a dull area about 5 centimeters in diameter to the right of the lower end of the sternum and continuous with the heart dulness. Heart sounds at the apex are of good quality. There is an inconstant systolic murmur over the pulmonic area, also over the aortic area. Lungs.—Expansion limited over right lower chest. Percussion reveals dulness at right base, extending almost up to the

¹ From the Roentgenological Service, Grady Hospital, Emory Division.

FIG. 1.



Cortical thickening.
Exostoses. Also bone
involvement over iliac
margin.

FIG. 2.



Right iliac bone involved.
Ankylosis of fourth and fifth
lumbar.

FIG. 3.



Right margins of lower thoracic
and all lumbar vertebrae anky-
losed. Left margins uninvolved.

FIG. 4.



Cervical spine uninvolved in this process.

FIG. 5.



Increased density right lower chest.

nipple anteriorly and up 2-3 centimeters posteriorly. Left chest resonant, no dulness. Fine crackling râles are heard along the lower right chest and in scattered areas above, from a line of the right nipple to lower angle of the scapula. The râles at the base are of a fine crackling type, those higher up seem to be of a fine moist type, and are more marked at the end of inspiration. Tactile fremitus not changed. No râles in left chest. Blood-pressure, 108/74; two days later, 100/80. Abdomen scaphoid in appearance. There is a spasticity of the right rectus muscle, the liver seems enlarged, about 1 inch below the right costal margin, surface smooth. There is tenderness on deep pressure over the subcostal area, about 1 inch below the ribs and especially noticeable over the gall-bladder region. The lumbar regions are tender on deep palpation. Fist percussion negative. Spleen and kidneys not palpable. Hernial rings OK. Glands.—Inguinals, axillaries, cervical and epitrochlears are firm and shotty, but not fixed or tender. Reflexes.—Hyperactive patellar and biceps. Others about normal. No ankle clonus or Babinski. Extremities.—Upper, negative. Lower extremities: Left negative. Right thigh shows many draining sinuses on the posterior lateral aspect, exuding a thick, yellow pus. There is tenderness and induration along the upper femur, which is most marked at the trochanteric levels. The tissue induration is brawny. Skin negative.

Summary.—1. Paleness of mucosa and nails (anemia). 2. General adenopathy. 3. Hypertrophy and dilatation of heart, with diffuse precordial pulsation. 4. Retraction of right chest wall. Dulness and few moist râles. 5. Enlarged liver with tenderness over the gall-bladder. 6. Dulness to right of sternum. 7. Tenderness in right lumbar region. 8. Draining sinuses in posterior lateral right thigh. 9. Cloudy urine since present illness. 11. Gonorrhoeal infection 1912.

Impression (Interne).—1. Osteomyelitis of right upper femur, with multiple draining sinuses. 2. Secondary anemia. 3. Chronic fibrinous pleurisy. 4. Dilatation and hypertrophy of heart, with possibility of adhesive pericarditis. 5. Pulmonary tuberculosis. 6. Secondary syphilis.

Laboratory Reports.—Blood Wassermann negative. Sputum.—No tubercular organisms found. A few diphtheroid organisms, many scattered staphylococci. He was referred for X-ray examination of right thigh.

X-Ray Report.—*Fig. 1.*—The upper third of right femur, near trochanters, is the seat of a chronic osteitis. The cortex is thickened, medulla not involved. Several bony exostoses project from the shaft into the soft tissues. At edge of the film we see evidence of bone destruction and production along the margin of the right iliac bone, occupying the area between the anterior superior spine and the superior border of the acetabulum. It is possible the primary focus is in this region. Return patient for further study.

Fig. 2.—Stereoscopic study of pelvis. There is a definite bone lesion along the margin of the right iliac bone, between anterior superior spine and superior acetabular margin. Bone production and destruction noted. There is ankylosis between the fourth and fifth lumbar vertebrae with dense bony spurs uniting their articular margins. This process extends higher. Return patient for study of spine.

Fig. 3.—From the mid-thoracic vertebra to the sacrum, all vertebrae are ankylosed along their right margins by dense bony spurs. This process is

FIG. 6.

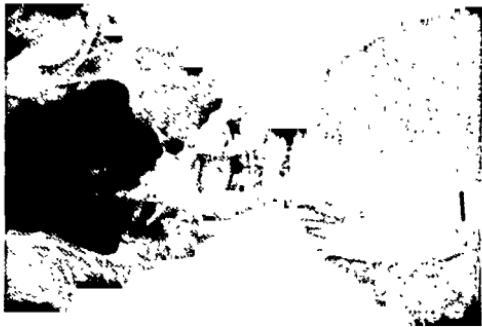
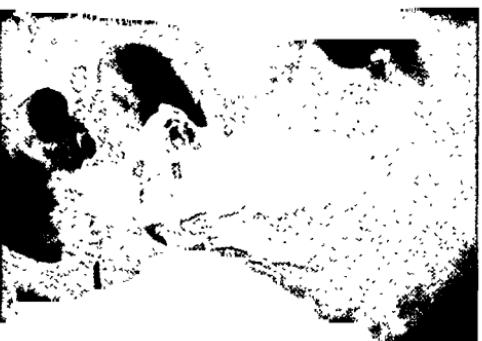


FIG. 7.



FIG. 8.



Course of Lipiodol from right lower chest, through diaphragm, into psoas fibers.

Lipiodol can be noted following the course of the psoas muscle, across the pelvis to mesial side of femur.

Three days later. Lipiodol still present in psoas muscle, in chest and over sacrum.

unilateral, hypertrophic in character and most unusual. The right lower chest is increased in density. Return for study of chest.

Fig. 4.—No bone change in cervical spine.

Fig. 5.—Stereoscopic study of chest. There is a marked increase in the density of the right lower chest. The diaphragm cannot be located. The lung is surrounded by a dense mass shadow at the base, which has a concave upper border, evidently fitting the lower surface of this right lung. The shadow is confluent with the heart. No displacement of heart or mediastinal structures.

Conclusions.—Empyema of right lower chest, which has drained through the diaphragm, downward through the psoas muscle and over the anterior longitudinal ligament, following the iliacus and psoas muscle sheaths across the pelvis with an accumulation of pus in and around the attachment of these muscles to the femur. It is suggested that the right base be aspirated and $\frac{1}{2}$ ounce of methylene blue be injected, to see if it will appear in the sinuses of the thigh, thus supporting this theory.

Before this report reached the ward he was discharged, having greatly improved, very little discharge and no pain. Eating and sleeping well. Realizing he could not continue well if the above conclusions were correct, he was re-admitted to the hospital for study November 7, 1930. On November 11 he was aspirated by Doctor Phillips; about 10 cubic centimeters of pus recovered. It had no odor. Laboratory report culture shows a short chain streptococci in diplo formation.

On November 13 he was again aspirated, 15 cubic centimeters of pus obtained and 30 cubic centimeters of methylene blue injected through the needle. This was done at 4 P.M. and the following morning, twelve hours later, it was noted on the dressings over the sinuses in his thigh.

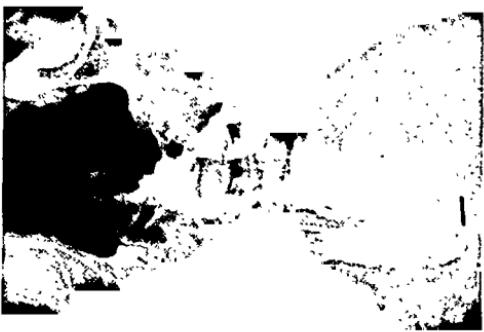
On November 15, 10 cubic centimeters of pus again aspirated and 15 cubic centimeters of lipiodol injected into chest. Patient removed to X-ray department for study.

Figs. 6, 7, and 8.—The iodized oil can be seen on the right diaphragm, also a pocket of oil behind the diaphragm in the 11th interspace. The tract of the sinus can be seen, apparently passing through the diaphragm, close to the spine and under the internal arcuate ligament. It then fills a large cavity in the body of the psoas muscle, draining downward, presenting a striated appearance, probably due to its course along the fibers of the psoas. In Fig. 7 a clot of oil can be seen over the right side of the sacrum. In a film made a little later, oil can be seen along the mesial side of the femur, near the lesser trochanter. Fig. 8 was made three days later, iodized oil is still present in the psoas muscle, near trochanters and in right lower chest.

November 21, 1930, he was operated by Dr. Dan C. Elkin. Under local anesthetic an incision was made along right posterior axillary line. About 3 inches of the ninth rib excised. The tissues were edematous, an infected sinus tract in the subcutaneous tissues ran down behind the twelfth rib. The pleural cavity explored. Pleura greatly thickened, tough and leathery, adherent to the lung. Drainage instituted. Biopsy of tissues removed. Inflammatory tissue—no evidence of tuberculosis.

A short review of the anatomy of this region will explain how an empyema may gravitate from the chest to the right thigh.

FIG. 6.



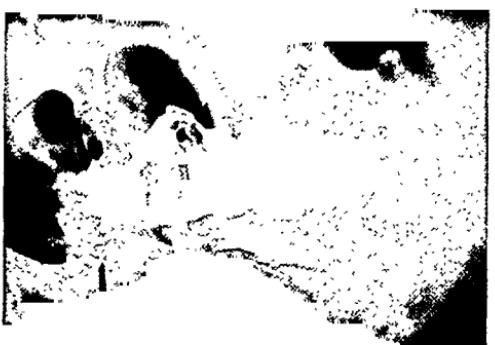
Course of lipiodol from right lower chest, through diaphragm, into psoas fibers.

FIG. 7.



Lipiodol can be noted following the course of the psoas muscle, across the pelvis to mesial side of femur.

FIG. 8.



Three days later. Lipiodol still present in psoas muscle, in chest and over sacrum.

The posterior fibers of the diaphragm arise from the anterior surfaces of the lumbar vertebrae by two crura. These are two elongated bundles of fibromuscular tissues, which arise from either side of the aorta from the anterior bodies of the lumbar vertebrae, on the right side from the first two lumbar vertebrae. They are directed upward and decussate across the median line, the fibers of the right crus passing anterior to those of the left. The psoas major arises from the vertebral column in the lumbar region. It takes origin from the intervertebral cartilages above each lumbar vertebra, and from the adjacent margins of the vertebrae, from the twelfth thoracic to the superior border of the fifth lumbar. It also arises from four aponeurotic arches which pass over the sides of the bodies of the first four lumbar and it takes additional origin posteriorly from the transverse processes of all the lumbar vertebrae. The fibers form a fusiform muscle which projects over the superior aperture of the pelvis passing behind the inguinal ligament to end in a tendon which is inserted into the apex of the lesser trochanter. The iliacus muscle arises in the pelvis major by fleshy fibers mainly from a horseshoe-shaped origin around the margin of the iliac fossa. It has additional origins from the ala of the sacrum and the anterior sacro-iliac, lumbo-sacral and ilio-lumbar ligaments, and outside the pelvis from the proximal part of the capsule of the hip-joint. It is a fan-shaped muscle and its fibers pass distally over the hip-joint to the lesser trochanter of the femur. The ligamentum longitudinale anterius consists of a wide stratum of longitudinal fibers which extend from the front of the first vertebra to the superior segment of the sacrum; it becomes gradually wider from above downward. It lies on the anterior surface of the vertebra and is attached to the anterior surfaces of the intervertebral fibrocartilages, as it passes from one vertebra to another. Its fibers vary in length.

"Abscess within the sheath of the psoas muscle is generally due to caries of the bodies of the vertebrae, lower thoracic or lumbar. When the disease is in the thoracic region, pus courses down the posterior mediastinum, in front of the bodies of the vertebrae and passing beneath the ligament arcuatum internum, enters the sheath of the psoas muscle, down which it passes as far as the pelvic brim.

It then gets beneath the iliac portion of the fascia and fills up the iliac fossa. In consequence of the attachment of the fascia to the pelvic brim, it rarely finds its way into the pelvis, but passes by a narrow opening under Poupart's ligament into the thigh, to the outer side of the femoral vessels." (Gray's Anatomy.)

By tracing these sinuses with iodized oil we may visualize the tract. This empyema entered the posterior mediastinum, also passed through the diaphragm, down along the anterior longitudinal ligament on the right and also through the fibers of the right psoas. It also entered the iliacus muscle, with resulting bone changes in all vertebrae along their right borders, the right side of the ilium and involving the femur near the lesser trochanter.

SUMMARY

Negro male complaining of pain over right hip.

History develops pneumonia in 1928 of seven weeks' duration, treated at home. Thought recovery complete. One year later pain in right hip. Cleared up under local treatment. One year later brawny swelling over right thigh. Treated as a localized abscess. Drained.

X-ray studies traced infection from hip to right chest. Aspiration plus injection of methylene blue confirmed diagnosis. Injection of iodized oil outlined sinus tracts from this empyema to the sinus over right upper thigh.

Operation—thoracotomy—disclosed empyema and abscess in deep structures of the back.

This case is presented on account of its many unusual features.

REPORT OF A CASE OF LARYNGEAL PAPILLOMA*

By CALHOUN McDougall, M.D. and EDWARD S. WRIGHT, M.D.
Atlanta, Georgia.

A COLORED boy, aged nineteen years, was admitted to the Grady Hospital Clinic complaining of a slight sore throat and hoarseness.

His history revealed that he had been hoarse for about five years and that for the past two years it had become markedly worse. At the age of thirteen he became the proud possessor of a cornet which he played frequently. About six months later a slight change was noticed in his voice but his parents, who are of the higher Ethiopian class and are school teachers in a negro college, thought that it was due to a normal change which occurs at puberty. Within the next three or four years the voice continued to become worse and the patient was taken to several doctors who prescribed sprays and gargles, to no avail.

In the last two years his voice became very husky, tired easily, resulting in almost complete aphonia at times. It was not until seven days before admission, when he contracted an acute coryza and sore throat resulting in progressive aphonia, that he sought further treatment.

On examination, the patient was found to have an acute coryza and nasopharyngitis, the inflammation extending downward. On indirect examination of the larynx both arytenoids and the laryngopharynx were slightly inflamed. The vocal cords were not visible. In their place were two elongated, reddish, elevated masses of tissue, almost meeting in the mid-line and leaving only a narrow glottis. There was only slight motility of these structures on respiration. It was impossible to tell whether the vocal cords were destroyed and incorporated in this tumor or were merely covered over. The right side appeared to be slightly ulcerated. A blood Wassermann test was taken and reported negative. Roentgenogram of chest was negative for any tubercular infection. His general physical condition was good.

The patient was admitted for a direct laryngoscopic examination on January 28, 1930. The examination revealed an irregular, reddish, granular mass of tissue on both sides of the larynx in the position of the vocal cords. There were no ulcerations. It had the appearance of a villous papilloma which was confirmed on histological examination.

This tissue was very firm and adherent and in order to prevent injury to the vocal cords had to be removed very carefully and skilfully. Instead of biting off the tumor mass it was scalped off with cupped forceps, removing a small amount at a time and scalping parallel with the cords. The right side was operated upon first, the mass being removed superficially, and the vocal cord was found to be intact beneath and was red in color.

At the same examination two small pedunculated tumors, arising from the anterior commissure and lying subglottic, were seen when the patient was made

* From the department of Oto-laryngology, Emory University, School of Medicine.

It then gets beneath the iliac portion of the fascia and fills up the iliac fossa. In consequence of the attachment of the fascia to the pelvic brim, it rarely finds its way into the pelvis, but passes by a narrow opening under Poupart's ligament into the thigh, to the outer side of the femoral vessels." (Gray's Anatomy.)

By tracing these sinuses with iodized oil we may visualize the tract. This empyema entered the posterior mediastinum, also passed through the diaphragm, down along the anterior longitudinal ligament on the right and also through the fibers of the right psoas. It also entered the iliacus muscle, with resulting bone changes in all vertebrae along their right borders, the right side of the ilium and involving the femur near the lesser trochanter.

SUMMARY

Negro male complaining of pain over right hip.

History develops pneumonia in 1928 of seven weeks' duration, treated at home. Thought recovery complete. One year later pain in right hip. Cleared up under local treatment. One year later brawny swelling over right thigh. Treated as a localized abscess. Drained.

X-ray studies traced infection from hip to right chest. Aspiration plus injection of methylene blue confirmed diagnosis. Injection of iodized oil outlined sinus tracts from this empyema to the sinus over right upper thigh.

Operation—thoracotomy—disclosed empyema and abscess in deep structures of the back.

This case is presented on account of its many unusual features.

REPORT OF A CASE OF LARYNGEAL PAPILLOMA*

By CALHOUN McDougall, M.D. and EDWARD S. WRIGHT, M.D.
Atlanta, Georgia.

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His history revealed that he had been hoarse for about five years and that for the past two years it had become markedly worse. At the age of thirteen he became the proud possessor of a cornet which he played frequently. About six months later a slight change was noticed in his voice but his parents, who are of the higher Ethiopian class and are school teachers in a negro college, thought that it was due to a normal change which occurs at puberty. Within the next three or four years the voice continued to become worse and the patient was taken to several doctors who prescribed sprays and gargles, to no avail.

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to pant, thus blowing the tumors supraglottic, then they were removed in this position.

The patient was discharged the next day and re-admitted on February 11, 1930. At this time the tissue was removed from the left cord in a similar manner. He was later admitted on March 3 and April 1 for removal of several fragments that remained.

Following the first operation there was a noticeable improvement in his voice and this continued after each succeeding operation. Each examination was performed under local anesthesia, a preliminary hypodermic of pantapon grains 1/3 with atropine sulphate grains, 1/150 being given thirty minutes before the operation and a 10 per cent. cocaine solution applied locally to the pyriform sinuses at the time of the operation.

At the end of eleven months there had been no recurrence in the larynx or other portions of the upper respiratory tract. The larynx now appears normal and the patient has a normal functioning voice.

Papilloma is the most frequent benign neoplasm of the larynx. There are two main types, the simple or single papilloma and the multiple or villous type of papilloma. They should always be considered potentially malignant but at the same time should be treated only as benign growths, unless proven definitely to be malignant, by histologic examination.

The single type consists of a single projection from the adjoining tissue, composed of a central core of connective tissue and covered with stratified squamous epithelium.

The villous type consists of innumerable small projections, bead- or granular-like in appearance, arising from a central base and covered with a similar epithelium of varying thickness.

Papillomata is considered a self-limited disease and no attempt should ever be made at radical removal. Such attempts always result in disastrous ruin of the larynx and loss of voice. Multiple papillomata have a strong tendency to repullate, not only at the original site but in remote locations of the larynx, fauces, nose and other places. The growth should always be removed superficially and the patient kept under observation. Only one cord should be operated on at a time. By doing this there is far less danger of obtaining laryngeal adhesions.

ON THE INDICATIONS FOR NEPHROSTOMY OR URETERAL TRANSPLANTATION INTO THE BOWEL

A REPORT OF A CASE OF SATISFACTORY URINARY DRAINAGE BY NEPHROSTOMY FOR SIX AND A HALF YEARS

By MONTAGUE L. BOYD, M.D.

Head of Department of Urology, Medical Department of Emory University

It is not the purpose of this presentation to advocate nephrostomy instead of ureteral transplantation into the bowel. Such arguments can well be left until the time when we have more data upon the relative advantages of these procedures. What I am trying to do is to call attention to the fact that urinary drainage by some method is indicated in many instances where it is not being established, and, by presenting the facts concerning one of my nephrostomy cases, to show what a wonderfully satisfactory result may be obtained, at least in certain patients, by nephrostomy.

The case which I am reporting here is an example of one of the rarer conditions in which it is possible to estimate more or less exactly the value of urinary drainage by nephrostomy when there exists a urinary obstruction in the lower ureter. Ordinarily, the patients upon whom nephrostomy or ureteral transplantation into the bowel is performed have cancer of the bladder, and the subsequent observations made upon the results of the operation for diverting the flow of urine are obscured by the effects which the patient suffers as the result of the presence of the cancer and its metastases, and also from the changes occurring in the bladder caused by a concurrent bladder infection. In this patient, however, there was only a complete block of the lower ureter caused by a stone, which was relieved by nephrostomy, and now for six and a half years he has worn a nephrostomy tube and, though the stones have remained in the ureter, they seem to have caused very little trouble. (Figs. 1-8.)

The available data upon the relative advantages of the different methods of diverting the urinary flow when a ureteral block, such as occurred in this patient or as occurs in cancer of the bladder involving the ureter, demands it, is not yet adequate for the formation

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of satisfactory conclusions which will enable us to know when to employ such urinary drainage and which method of operative procedure to choose. Yet the need for such data must be evident to every one; certainly it is most evident to those who are interested in cancer of the bladder and of the prostate, where urinary drainage is indicated far more frequently than it is being established.

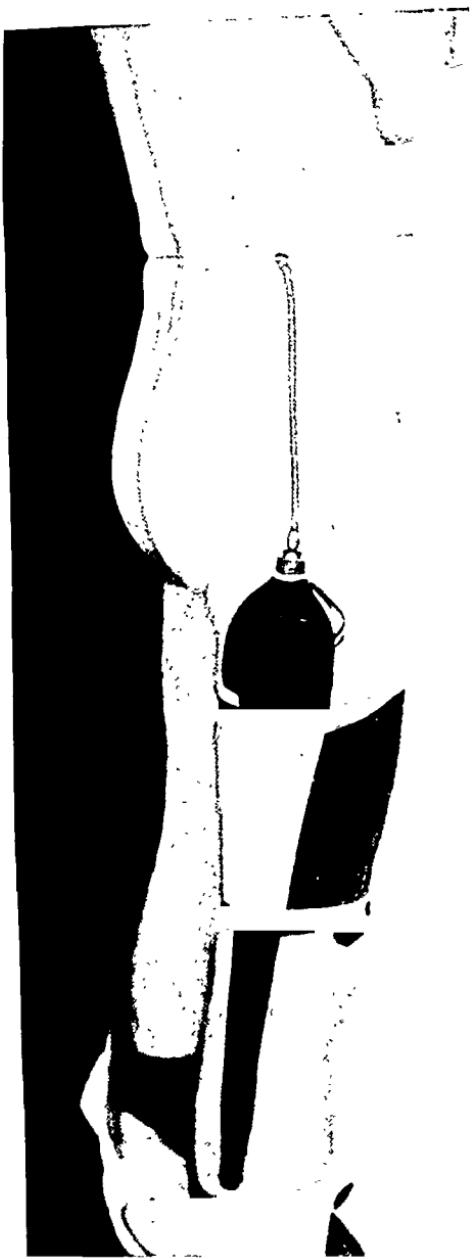
Briefly, the most common conditions in which indications exist for diverting the normal course of the urinary flow through the bladder are:

- (1) In total cystectomy.
- (2) In partial cystectomy where so much of the bladder or so much of the lower end of the ureter (or both) is removed that it is not possible to transplant the ureter into the bladder.
- (3) In inoperable cancer of the ureter or bladder with ureteral obstruction which cannot be relieved at all or only after a long time.
- (4) In irreparable injuries to the ureter.
- (5) In hydronephrosis caused by irreparable, acquired or congenital changes of the kidney pelvis or the upper end of the ureter. (Certainly in some of these cases, where, for example, there are bilateral changes or where there is only one kidney, nephrostomy is indicated rather than some plastic operation. Or both operations may be performed and the nephrostomy tube left in as long as necessary if the plastic operation is not a success.)
- (6) In marked ureteral obstructions where the obstruction for any reason cannot be relieved with certainty or sufficiently promptly; *e.g.*, stone in the ureter, cancer of the prostate, or obstruction of the ureter by extra-ureteral diseases.

There will, without doubt, be some who will disagree with me concerning the necessity for or the desirability of performing a nephrostomy or ureteral transplantation into the bowel in at least some of these conditions. For my part, however, I am sure that in time we shall establish urinary drainage in many patients who are now not considered suitable subjects for that procedure and are consequently being permitted to suffer as the result of unrelieved obstructions.

CASE 1271 A.—D. G., aged twenty-two, single, student. The patient was a coöperative student in one of technologic schools of the south, with very little money, and, as he was eager to keep on with his work at school, the treatments

FIG. 1.



(November 11, 1930.) Showing the nephrostomy tube held in place by a piece of cord which is tied about the patient's waist. The tube is connected directly to the bag, and just below that point the tape, by which the bag is suspended from the patient's shoulder, is seen tied about the top of the bag.

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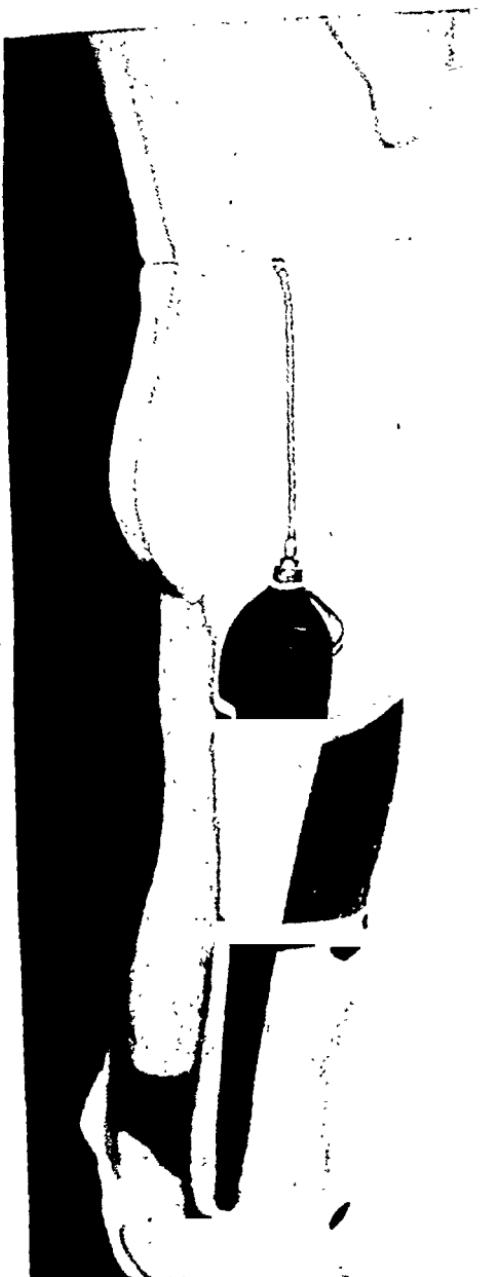
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FIG. 2.



January, 1853.) Showing the shadow of the urethral stone which was removed by crushing with a lithotrite.

B. V.

given him and the operations which I performed for him were made to accord with his ability to be away from school and to pay for hospitalization, except, of course, in emergencies.

On December 23, 1921, he was brought to me, suffering with an acute attack of left pyelonephritis which had existed for about six days. He had had and was having fever, nausea, vomiting, and felt quite sick. Examination showed that he had a stone about 3 centimeters in diameter in the left ureter, just outside the bladder wall (Fig. 3) and an acute left pyelonephritis with an almost completely destroyed left kidney. He also had a stone (Fig. 2) about 1 centimeter in diameter in the bulbous urethra, lying just back of a moderately firm, fibrous stricture of 27 French caliber. An intramuscular injection of 6 milligrams of phthalein and catheterization of the right ureter showed an output in one hour of 12 per cent. on the right and 5 per cent. from the bladder; the appearance time on the right was nine minutes. The right kidney was not infected.

The past history was unimportant except as follows: From early childhood until twelve years of age he was troubled with bed-wetting and with attacks of retention of urine, lasting often for ten to twelve hours and accompanied by a good deal of pain, due apparently to the overdistention of the bladder. These attacks came on at intervals of one or two days or of two or three weeks. With them he would sometimes pass small quantities of blood from the urethra, but he could not recall whether or not an increased frequency of urination existed. At the age of twelve an "external urethrotomy" was performed for the removal of a stone from the bladder. He recovered readily and remained well until three years ago (aged nineteen) when he had an attack of acute pain in the left kidney region which lasted about twenty-four hours and was severe enough to require the administration of morphine. From this time he was perfectly well until the beginning of the present illness about one week ago.

PROGRESS NOTES

The acute pyelonephritis subsided in a few days and a total intramuscular phthalein test then showed, on voiding, an appearance time of ten minutes and an output of 25 per cent. in the first hour and 20 per cent. in the second hour.

The urethral stone lay in a fairly large pocket which had formed in the bulbous urethra, where it had been opened when he was twelve years old for the removal of the bladder stones. It was possible, therefore (January 20, 1922), to crush the stone with a lithotrite and wash out the fragments.

During the following five months the patient was treated by a usage of the prostate and seminal vesicles, dilatations of the urethra, urinary antiseptics, and occasional ureteral dilatations. His general condition improved and he had no acute exacerbation of the chronic infections in the left kidney and bladder.

On June 20, 1922, I attempted to remove the ureteral calculus from the lower end of the left ureter through a suprapubic cystotomy wound. Unfortunately, during the night preceding the morning set for the operation, he developed a more or less complete left ureteral block (with renal colic) so that the largely dilated ureter above the stone was filled with urine, and so permitted the calculus to slip back up the ureter beyond my reach when, after widely opening the lower end of the ureter, an effort was made to grasp it with a pair

of ureteral stone forceps. The patient was in a modified Trendelenburg position and the stone went back up the ureter so far that it was not possible to reach it, even though the position was reversed.

On November 11, 1922, I performed a left nephrectomy, and on June 16, 1923, I removed the left ureter which still contained the stone. The lower end of the ureter near the bladder was very adherent and its complete removal was almost impossible (Fig. 6).

During this time (eighteen months from admission) the right kidney seemed to be all right—uninfected, and with normal drainage (ureteral catheterization and urogram). Its function rose to about normal (a 26 per cent. 'phthalein output in one hour and fifteen minutes after intramuscular injection) and the numerous roentgenograms showed no shadows suggesting stones in the right kidney or ureter. However, in April, 1923, he began to have attacks of right renal colic and examination disclosed a streptococcus infection and a stone in the right kidney pelvis (Fig. 4). Short attacks of pain from the calculus in the right kidney recurred persistently and he had an occasional elevation of temperature with the attacks. X-rays of his teeth showed no apical infection, although he did have a slight pyorrhea. The blood chemistry was normal. The right kidney function obtained in October was 10 per cent. for the first hour after an intramuscular injection and 15 per cent. for the second hour. On October 27, 1923, a pyelolithotomy was performed, the stones being removed with very little difficulty. The roentgenograms taken at this time show no shadow of ureteral stones, but it was evident that drainage from the kidney was not good and ureteral dilatations, with kidney lavage and urinary antisepsics, were continued in hopes that the kidney infection which persisted after the pyelolithotomy could be cleared up. In spite of these precautions, the patient had another attack of right renal colic in December, 1923, and a ureteral obstruction was found, to an 8 French catheter, at about 12 centimeters, but even then a roentgenogram (made December 19, 1923) showed no definite shadow suggesting stone in the ureter. An intramuscular 'phthalein test showed 15 per cent. the first hour and 15 per cent. the second hour. But on March 5, 1924, a roentgenogram showed two rather faint shadows in the region of the lower ureter, one about 1.5 centimeters in diameter and the other about 1.2 centimeters (Fig. 5). A urogram made on April 9, 1924, is shown in Fig. 6. On April 25, 1924, a sudden and complete urinary blocking occurred which could not be relieved by ureteral catheterization so the kidney was exposed at once through a loin incision and a 30 French drainage tube left in the pelvis through the lower major calyx (Fig. 7).

SUBSEQUENT HISTORY

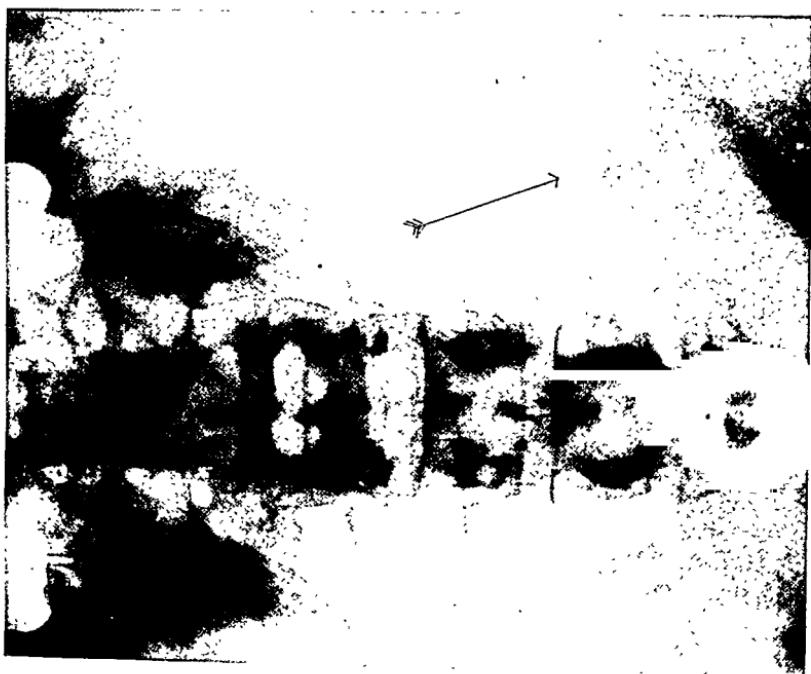
Since the nephrostomy the patient has gradually improved. He has had very little trouble with the drainage tube except on a few occasions when the tube, after being allowed to slip out, was not replaced immediately. When that happened the wound closed down in a few hours to a point where it was difficult to reinsert the tube. He has returned once or twice a year for observation and came back on November 11, 1930, at my request. The photograph shown in Fig. 1 was taken at that time, and the roentgenogram in Fig. 8 was also made. An intramuscular 'phthalein test showed an output of 26 per cent. in the first hour, and the patient was in better health than he had been at any

FIG. 3.



(June 15, 1922.) Showing the shadow of the stone in the lower left ureter before the left nephrectomy. The ureter and stone were removed June 16, 1923.

FIG. 4.



(April 27, 1923.) Showing the shadow of the stone in the right kidney, removed by operation on October 27, 1923.

FIG. 5.



(March 5, 1924.) Showing the shadow of the two stones in the lower right ureter, which are also seen in the roentgenogram made November 11, 1930 (Fig. 8).

FIG. 6.



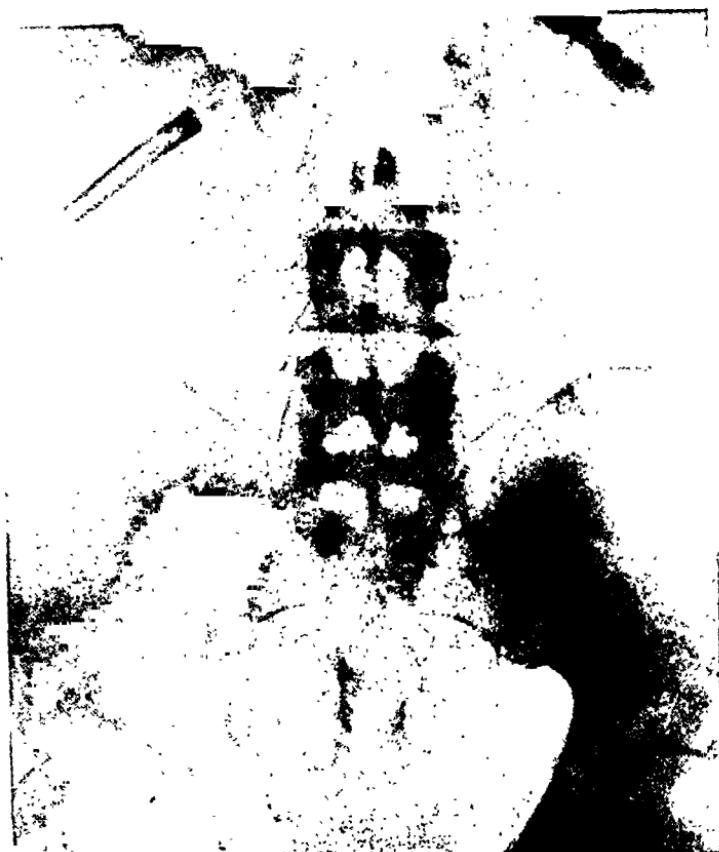
(April 8, 1924.) A urogram showing the remaining portion of the left ureter filled with the sodium iodid which ran back from the bladder. Two undilated portions of the right ureter are seen. The stones, of course, lie in the dilatation in the lower part of the ureter.

FIG. 7.



(August 14, 1925, sixteen months after the nephrostomy) Showing the position of the nephrostomy tube in the kidney. The ureter is readily filled as far down as the stones, even when only a small amount of iodid is injected. Much the same conditions in the kidney and ureter were to be seen in the roentgenograms made before and since the date when this roentgenogram was made.

FIG. 8.



(November 11, 1930.) Showing the condition now existing—the position of the tube, the absence of stones in the kidney and *the decrease in size of the shadows of the stones in the lower ureter*. Compare the shadows here with those in Fig. 5.

time since the nephrostomy. Shortly after the last operation he was married, and he tells me that his sexual functions are normal though he has had no children.

It is interesting to note that the patient's bladder has given him very little trouble since the nephrostomy operation. He voids very infrequently but occasionally the tube is blocked off by his lying on it when he is asleep, and the bladder becomes partially filled. Three months after the nephrostomy the bladder capacity was found to be 280 cubic centimeters. In December, 1925, he voided 150 cubic centimeters during one of the times when he had difficulty in replacing the nephrostomy tube, and at his last visit, November 11, 1930, he informed me that he occasionally voided as much as 120 to 150 cubic centimeters at one time.

The tissues about the tube have always been healthy looking and clean, and it was only during the first few months after the tube was put in that there was even a small deposit of urinary salts on the end of the tube which was in the kidney.

COMMENTS

There are records in the literature of other cases where urinary drainage by nephrostomy has been carried on for much longer periods than the one I am reporting here; in some instances both kidneys have been very satisfactorily drained in that way for many years, but even if the period of drainage in this patient has not been so long I feel that the patient has had such a happy result that his case is well worth reporting.

The most interesting thing to me in this patient is the fact that there was an immediate cessation of stone formation as soon as free drainage of the kidney pelvis was established. It is most excellent evidence in support of the well-known fact that urinary obstruction has so much to do with the formation of urinary stones, and it would appear here to have been an essential factor because nothing other than the nephrostomy seems to have influenced the stone formation; no teeth were pulled, no tonsillectomy performed, etc., and no change made in the patient's habits of living. Even the drainage tube has been remarkably free from the deposit of urinary salts which at the time of the operation I expected to give us later on a great deal of trouble. I am not prepared to explain this complete cessation of stone formation, but in view of the fact that he was rapidly forming stones in the urinary tract before the nephrostomy I certainly expected the process to continue as long as he had a foreign body like a tube in the kidney.

I have been surprised also by the patient's good health since the nephrostomy, and his ability to go in a seemingly normal fashion about the affairs of life—get married, successfully conduct a business, and remain in good physical condition.

The simple method of keeping the nephrostomy tube in place with a piece of cord tied around it and fastened around the patient's waist has been eminently successful with my patient; it is a clean and comfortable way of keeping the tube in position, but I doubt that it would prove so effective in a patient with a large or flabby abdomen. The drainage of the urine into the bag of an ordinary rubber urinal as shown in Fig. 1, has also proven quite satisfactory in this patient and in one or two others where I have tried it. An ordinary rubber urethral catheter about 26 French is used for the nephrostomy tube and it is connected directly, in most cases, to the rubber bag of the urinal. To prepare the end of the catheter which is left in the kidney pelvis, the rounded end of the catheter is cut off and an eye made in the side about one centimeter from the cut end; the edges of these cuts are then burned with a piece of heated metal until they are smooth and soft and the burned area then cleaned with gasoline. At first I insisted that the tube be removed and cleaned at least once a week, but he does not now seem to find it necessary to change or clean it more often than every three weeks.

For a long time I felt that no operation for the removal of the ureteral calculi was indicated in this patient because he had been through so much and because I felt that the best chance to save his remaining kidney was to have the freest possible drainage for the urine. But for several years now he has been so well, and the kidney and ureter so nearly normal (Fig. 7), and the kidney function has remained so high, that I have been in favor of removing the ureteral calculi. If that were done the nephrostomy tube could be still left in and after the patient recovered from the operation it could gradually be closed off for periods of increasing length while a careful lookout could be kept for signs of a return of the tendency to the formation of urinary stones. The advantage which the nephrostomy tube affords by employing it in this way seems to me an argument for the performance of nephrostomy in certain cases where the need for continuing the drainage may last for only a comparatively short time.

COMPLETE GASTRIC RETENTION FOLLOWING GASTROJEJUNOSTOMY

(Cured by a Second Gastro-enterostomy)

By LON GROVE, M.D.

Atlanta, Georgia

MR. C. B., farmer, aged 47, was admitted to my service at Wesley Memorial Hospital, May 21, 1928, with a diagnosis of gastric ulcer.

History.—Seven years previous, at 10:00 P.M. after a hard day's work, he vomited a large amount of blood. On the following day he again vomited blood. He was brought to Atlanta and placed under the care of an internist who made a diagnosis of gastric ulcer. He was put on a strict medical régime, and was not allowed to return to work for a year. During the time that intervened, which was approximately seven and one-half years, he remained under the care of a physician, and there was no recurrence of hemorrhages, but there were periods during which he suffered some pain. The pain bore a definite relation to meals, was described as gnawing in character, and was relieved by soda. Three days before admission to the hospital, he again vomited a large amount of blood.

The family history was negative for tuberculosis and cancer, and his past history was unimportant.

Examination.—He was well-developed, with no marked loss of weight, but he showed definite evidence of anemia. The blood study showed definite evidence of a high grade secondary anemia; red blood count being 2,400,000, white blood count 18,000, with hemoglobin of 50 per cent. The blood Wassermann was negative and examination of stool was positive for occult blood.

He was transfused, 500 cubic centimeters of whole blood, by the Lindeman method, and in addition received the usual treatment prescribed for one with acute gastric hemorrhage.

On May 28, seven days after admission, fluoroscopic and X-ray studies were made with the following conclusions: "Probably carcinoma of the pyloric end of the stomach, but considering the long ulcer history, it is possible that we are dealing with a large saddle ulcer of the lesser curvature, with a resulting deformity." (Fig. 1.)

On June 6, under gas-ether anesthesia, the abdomen was opened, and a saddle ulcer of the lesser curvature was found. The pyloric end of the stomach was found to be entirely normal. The ulcer was excised by the usual technic, as shown in Fig. 2, exhibit A, and following this a posterior no-loop gastro-enterostomy was done, the stoma being made low on the posterior wall of the stomach, well toward the pylorus. (Fig. 2, exhibit B.)

For three days following operation his convalescence was uneventful. On the afternoon of the fourth day, he vomited a large amount of blood-stained fluid, and he continued to vomit everything taken by mouth until June 18, date of the second operation. He vomited only once or twice during the twenty-four

hours, but large amounts. During this time, a period of ten days, there were no symptoms of toxemia, such as would be expected from an obstruction of the duodenum. His fluid intake was kept up by subcutaneous injections of saline and glucose, approximately 2000 cubic centimeters a day.

On June 13, seventh postoperative day, a fluoroscopic and X-ray study was again carried out with the following findings: "The lower portion of the stomach from the incisura to pylorus is in a state of marked spasm. I am unable to fill or distend this area and no barium passes through gastro-enterostomy." He was given 1/50 of a grain of atropine, and examination two hours later showed the same condition existing. (Fig. 2, exhibit C.)

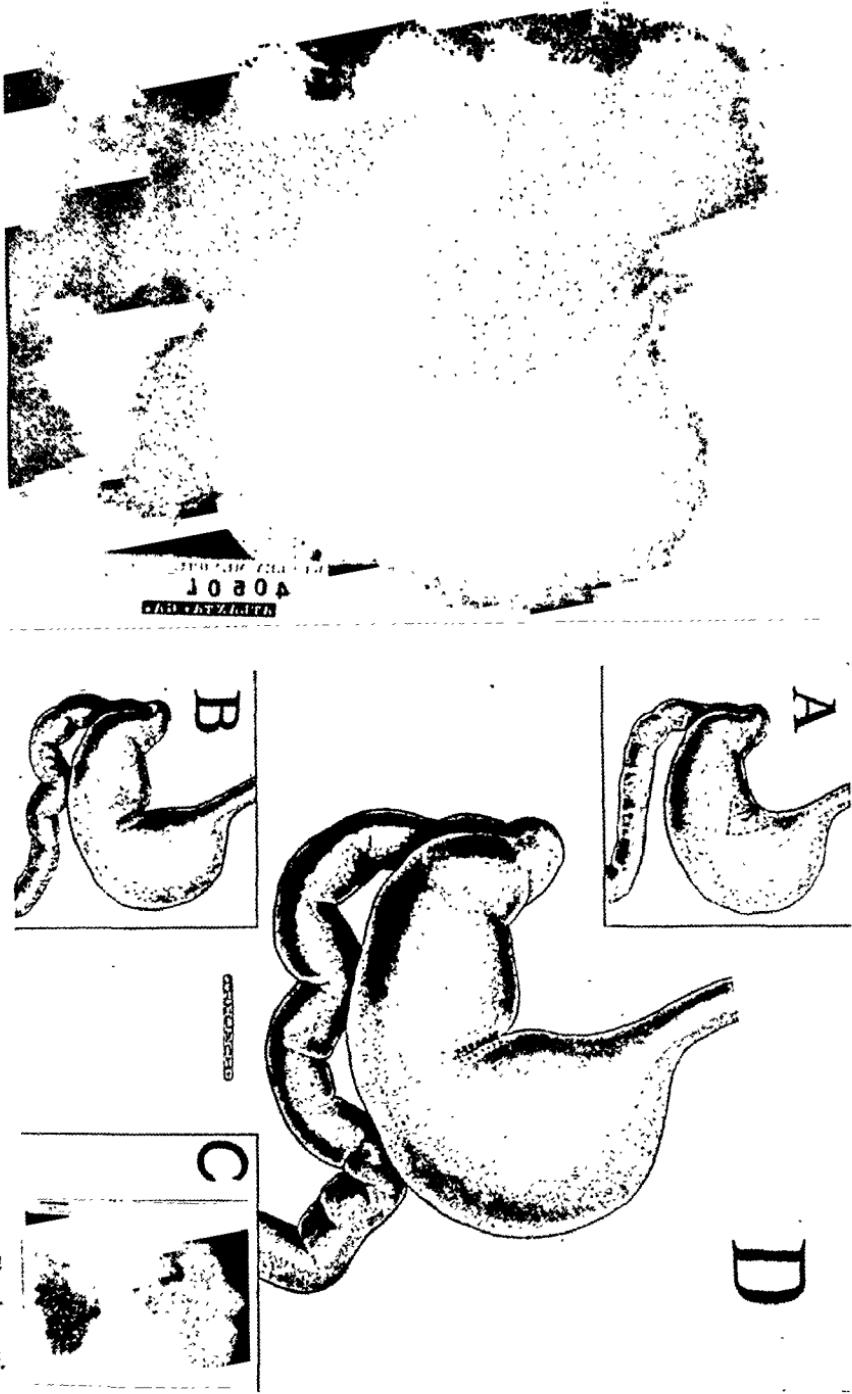
Three days later, June 16, under gas-ether anesthesia, the abdomen was again opened, through a left rectus incision. Examination showed the previous gastro-enterostomy to be in good condition, and so far as could be determined there was no angulation or cause for obstruction. Being of the opinion that the stomach did not empty, because the contents of the stomach could not reach the gastro-enterostomy stoma, a second gastro-enterostomy was decided upon, selecting a point high on the posterior wall of the stomach, as the point of anastomosis. (Fig. 2, exhibit D.)

Following the second operation, convalescence was uneventful and patient did not vomit. With the usual postoperative care, he made an uneventful recovery and was dismissed from the hospital June 28, the twelfth postoperative day.

Subsequent Note.—Patient has been seen from time to time, and has remained in good health. There has been no return of gastric symptoms and stomach appears to be functioning well despite double gastrojejunostomy. X-ray and fluoroscopic study done January 1, 1930 revealed the following findings: "Stomach is normal in size and position. There appears to be a double gastro-enterostomy with barium meal passing through both openings; 2-hour examination shows no barium passing through the pylorus; 4-hour examination shows a very slight residue remaining in stomach and head of barium is in the cecum, with major residue in terminal ileum." (Fig. 3.) Motility appears to be more normal now and both stomata are functioning, but no barium is passing through the duodenum.

Discussion.—This case is of interest because, when confronted with a complication such as described, a subsequent gastro-enterostomy appears to be the simplest and safest procedure. Had we attempted a degastrojejunostomy we would have encountered a friable suture line which probably would have been troublesome, and had this been managed successfully we still would have been confronted with a stomach which could not empty. The case is of further in-

FIG. 1.



Showing marked deformity of the pylorus before operation.

A.—Site of ulcer of lesser curvature; line of excision. B.—Showing position of stoma of first gastro-enterostomy. C.—No barium appears to reach gastro-enterostomy opening or pylorus; barium is floating in gastric content. D.—Position of second gastro-enterostomy opening with respect to site of ulcer.

FIG. 3.



Stomach is emptying through both gastro-enterostomy openings; none appears to be passing through the duodenum.

terest because it appears to lend clinical proof to the contentions of Alvarez and Klein, who believe that gastric peristalsis begins in a nodal center in the lesser curvature of the stomach, near the pylorus, and is transmitted along the lesser curvature. They think therefore, that normal conductivity of the gastric peristalsis is dependent on the lesser curvature and any disturbance of this nervous mechanism, whether due to inflammatory reactions or to mechanical causes (as was produced in this case by excision of the ulcer) results in a marked disturbance of the motility of the stomach. It would appear that the first gastro-enterostomy stoma was not obstructed, but being low on the posterior wall it was not reached by the peristalsis of the stomach, or if reached the peristalsis was too weak to deliver the gastric contents into the stoma, therefore the stomach could not empty. Horsley has called attention to the importance of preserving the lesser curvature whenever possible, and when sleeve resection is necessary, care should be taken to re-align the lesser curvature, at the expense, if needs be, of the greater curvature. This precaution should also be observed when suturing the stomach to the duodenum. As shown by this case, when an ulcer of the lesser curvature is excised it is important to make the stoma above the line of excision, in order that it might receive normal peristalsis. The effect of an irritating lesion of the lesser curvature is also well demonstrated by this case. The ulcer on the lesser curvature produced such deformity of the pylorus as to give rise to a diagnosis of a probable malignancy, in that area. (Fig. 1.) From the Surgical Department of Emory University.

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OSTEOGENIC SARCOMA OF TIBIA

By F. G. HODGSON, M.D.

Atlanta, Georgia

THIS case is reported because it presents some unusual features. It was discovered fairly early, and due to the coöperation of clinician, radiologist, and pathologists a diagnosis was made and an amputation performed. In five months the patient was back on his job wearing an artificial limb. He is apparently well. No signs of recurrence more than six months following operation.

L. F. B., white, male, aged 25, mill worker, admitted to Wesley Hospital Clinic March 28, 1930. About three weeks ago patient bumped left shin against beam. This did not hurt very much. He kept on at work, but several days later, leg began to pain and ache. The pain seemed worse when he was off his feet. There was nothing in his family history or past history of importance. He denies venereal infection. Has had no fever. He walks with a slight limp. There is a little swelling and marked tenderness over upper third of left tibia. Physical examination otherwise negative. Icthyol ointment was applied.

X-ray Report (Figs. 1 and 2).—In upper third of tibia is an area of bone destruction, about 1 inch in diameter. The inner border of cortex is expanded and partially eroded. There is no definite periosteal reaction. The radiologist's conclusions were: (1) infection; (2) lues; malignancy; or (4) bone cyst.

When patient returned to clinic one week later, pain had continued and was the same, swelling of bone seemed a little larger, some increase in local temperature. He was advised to enter hospital for further study and observation. Wassermann and Kahn tests were negative. Blood essentially normal, urinalysis negative. No Bence-Jones proteid. Another X-ray taken April 10, 1930, ten days after the first (Figs. 3 and 4) shows a distinct increase in the destruction in the medulla, the cortex is further eroded, and a beginning invasion of the soft tissues is noted. The radiologist is in favor of a malignant tumor, a secondary carcinoma rather than a sarcoma. No metastasis in lungs. At this time the tumor could be felt extending about 1 centimeter beyond the inner border of the tibia. It was distinctly pulsating. The heart-beat could easily be counted by keeping a finger on the tumor. Several surgeons saw this man and the consensus of opinion was that it was a malignant bone tumor, type undetermined.

April 14, 1930, under ethylene anesthesia, a tourniquet was applied. An incision over swelling revealed a fairly well-encapsulated tumor, extending about 1 centimeter beyond cortex, grayish in color, very soft. A small piece was removed and given to pathologist for a frozen section. His diagnosis was malignancy, probably sarcoma (Doctor Kracke), so an amputation was performed through lower end of femur. Convalescence was uneventful.

Pathological Report (Dr. E. L. Bishop, Consulting Pathologist to Wesley

FIG. 1.



FIG. 2.



Antero-posterior view. X-ray made March 31, 1930. First X-ray made March 31, 1930, lateral view.

FIG. 3.



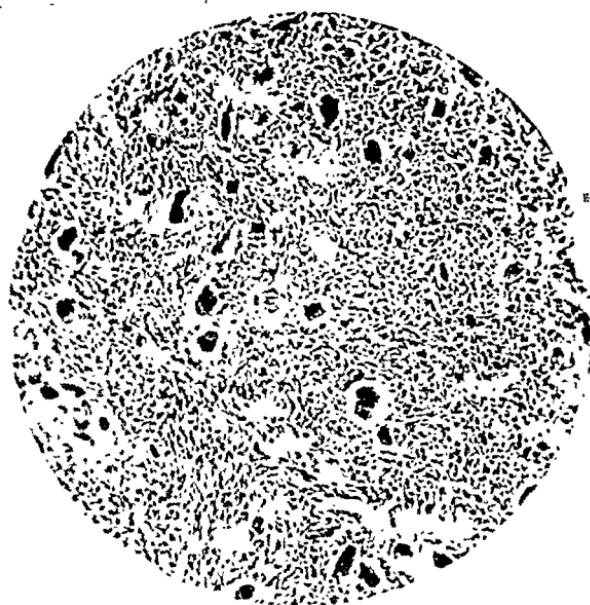
X-ray made April 10, 1930, showing increase
in destructive process.

FIG. 4.



X-ray, April 10, 1930, showing destruction
of cortex.

FIG. 5.



Cellular fibrous stroma with many "foreign body" giant cells.
Resembles benign giant-cell tumor.

FIG. 6.



Cellular structure with "tumor" giant cells and traces of osteoid tissue.
Diagnosed osteogenic sarcoma.

FIG. 7.



Gross specimen showing more extensive growth and destruction than indicated in radiograms.

Memorial Hospital).—"Specimen consists of an upper portion of the tibia, which has been split in two, showing a tumor mass in the upper third of the bone, 5 centimeters in diameter. The tumor is centrally located and has destroyed the bone to the outer layers of the cortex which is expanded but without any elevation of the periosteum. There is some dark discoloration in the medullary cavity extending downward from the tumor. Grossly, the tumor is very friable and vascular altho there are bony spicules thruout the tumor. The sections show a very interesting picture. The tissue from the central portion shows a very rich vascular stroma which is also very cellular and contains great numbers of foreign body giant cells. The stroma cells themselves are hyperchromatic and suggest malignancy at once, altho the large numbers of giant cells of foreign body type make one think of a very cellular and not entirely benign Giant Cell tumor. Sections from other portions show less of the giant cell structure and more of smaller and intensely hyperchromatic spindle and polyhedral shaped cells with a number of mitoses. No bone formation is seen and little of hyaline structure. Numerous true tumor giant cells and tumor blood vessels are found in these areas. Diagnosis: Osteogenic Sarcoma."

We see from the photomicrograph (Fig. 5) that a single frozen section from this tumor might easily be mistaken for a giant-cell tumor. The X-rays, however, are not like a benign giant-cell tumor. The other microphotograph (Fig. 6) shows malignant osteogenic sarcoma. This illustrates the importance of making sections from more than one area of the tumor to make a definite diagnosis. The numerous large blood spaces show why the tumor mass pulsated. This might put this tumor under the old classification of *malignant bone aneurysm*—this, however, is a poor name as it has no characteristics of an aneurysmal tumor. The radiograms show definite bone destruction, with little or no production or periosteal change. This would put this tumor under the osteolytic type of osteogenic sarcoma.

The patient and his friends tried to get me to give them a statement to the effect that the trauma, bumping his shin, was the cause of the tumor, hence the cause of the loss of his leg. This would entitle him to compensation. It is quite possible that the tumor existed prior to the trauma. No one can say definitely the relation of trauma to these cases. It would be very difficult, however, to prove to a jury that the trauma was not the cause of this tumor.

This patient has reported back to the clinic at regular intervals. He wore a stump shrinker for one month, then was fitted with an artificial limb. On September 5, 1930, he reported that he had worked eleven hours without discomfort. There is no evidence of recurrence either locally or in the lungs.

REPORT OF A CASE OF LIPOMYXOSARCOMA

By W. A. SELMAN, M.D.
Atlanta, Georgia

Mrs. O. W. H. of Flowery Branch, Georgia, was referred to me by Dr. M. B. Allen of Hoschton, Georgia, on May 7, 1926. White, age 20, married, two children, five and seven years, school teacher.

Chief Complaint.—Discovered a mass in the right side of her abdomen three weeks ago.

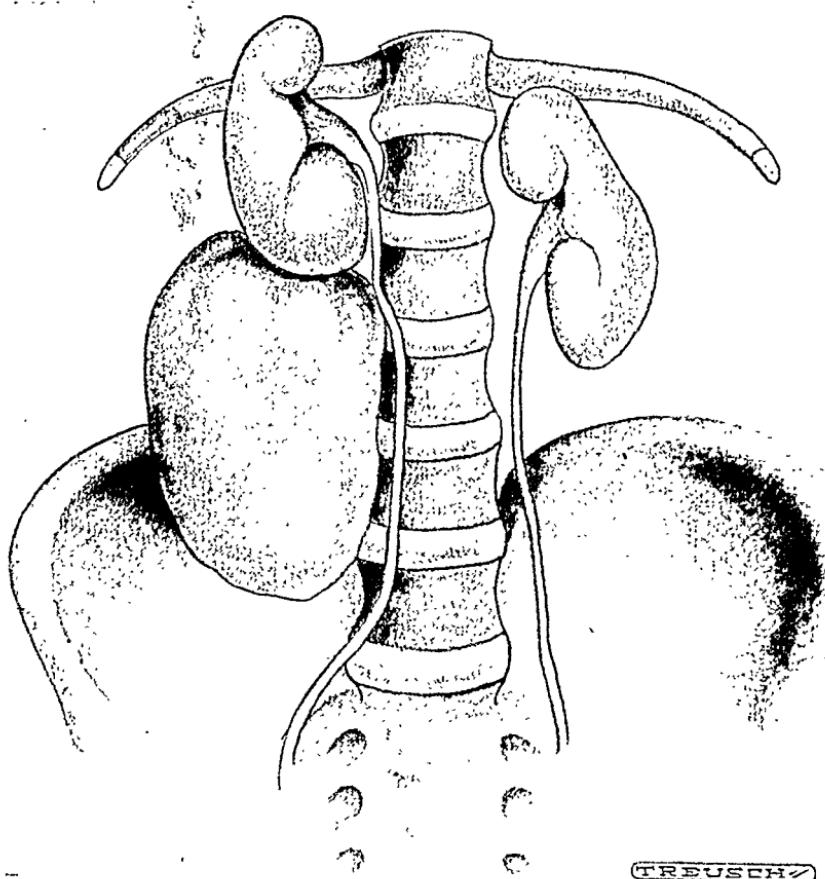
Family history unimportant, except that one grandmother and several aunts had died of cancer of breast or uterus.

Past History.—Measles, mumps and whooping cough in childhood. "Flu" in 1917. Two normal pregnancies, no complications. For the past year, especially during menstrual periods, she has had a bearing down feeling in the lower abdomen. At times she becomes nervous and weak, but has very little pain. She consulted her local physician and was found to have a retroverted uterus with an erosion of the cervix, for which she was treated with improvement. For the past six months she has had to get up once at night to void and an increased frequency during the day was noticed. This was not accompanied by pain or burning and no blood was seen.

Present Illness.—About three weeks ago she felt a hard mass in the right side of her abdomen. There was no pain, but noticing her right side was larger than the left, she discovered she had this hard round tumor. She also noticed the increased frequency of urination. Her weight is 147, which is normal for her. Appetite good; eats anything she desires. At times constipated, but usually remedies that by eating fruits. Blood-pressure 114/58.

Urological Examination, made by Dr. Earl Floyd, was as follows.—After preliminary preparation and small hypodermic of morphine, the cystoscope was passed into her bladder and a bladder specimen of urine collected. On distention of the bladder with fluid it was found to be fairly normal except in the region of the trigone on the right side. Here, for a distance of a centimeter it was quite red with a thin layer of mucus covering it. The left orifice was easily found; in normal position and appearance. It was with some difficulty that the right one was found. After searching for about fifteen minutes it was found just back of the congested area mentioned above; a little out of its normal position. A lead catheter was passed up both ureters and specimens of urine were collected. It dripped very slowly for a while, but I think this partly due to the fact that she had drunk but little water prior to the examination. After collecting a small specimen and pressing on the tumor mass in her right side to see what effect it had on the flow and the color of the urine, she was given 1 cubic centimeter of phthalein intravenously and the appearance time noted. The dye appeared on the left side in five minutes; right side, eleven minutes. Specimens were collected for fifteen minutes from the time of appearance on the left side. Output left side, 9 per cent., right side, 5 per cent. Examinations of specimens microscopically—right specimen showed a moderate number of red blood cells

FIG. 1.



TREUSSCH

Relation of tumor to right kidney and ureter.

FIG. 2.

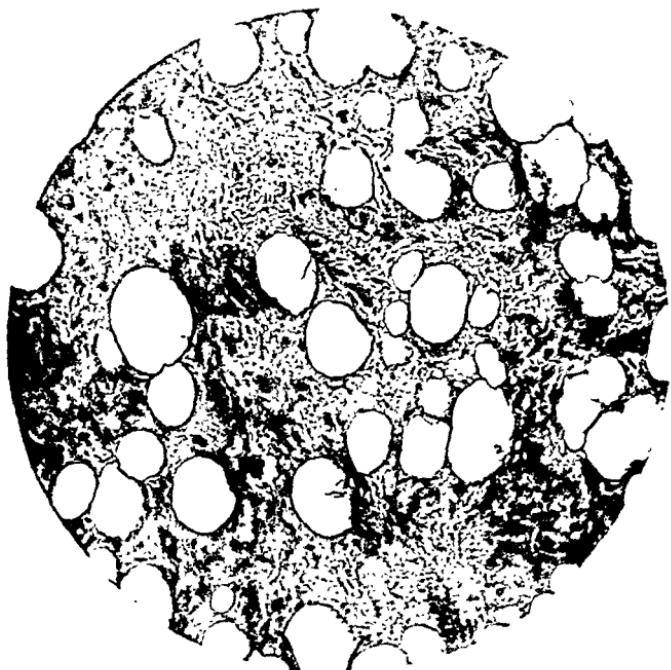
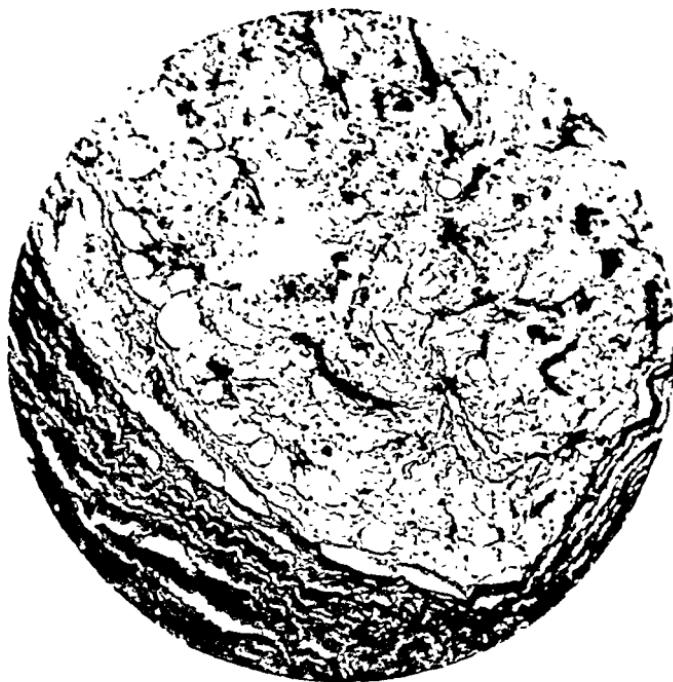


FIG. 3.



Microscopic appearance of the lipomyxosarcoma.

Microscopic appearance of the lipomyxosarcoma.

and many epithelial cells, no organisms and a rare leucocyte; left specimen showed a few epithelial cells. She was sent to the X-ray room with catheters *in situ* for pyelogram. A picture was taken before injecting in order to get the position of the catheters. It is not good policy to do a double pyelogram, but in this particular case we felt justified. Ten cubic centimeters of sodium iodide were injected through right catheter and 6 in left.

Interpretation of Plate.—Both kidneys seen, left lower than right. The lower pole of the right one was turned in and extended to the lower border of the second lumbar vertebra. The lower pole of the left extends to the upper border of the third lumbar vertebra. The right pelvis is a little dilated and there is a tendency of the calyces to club. The left pelvis is normal and the calyces show normal cupping. The right ureter is pushed across toward the mid-line and along the lower vertebra it is in the middle and shows a little dilatation. The left is normal (Fig. 1).

Conclusion.—This is not a primary growth of the kidney nor is it connected with the kidney. It has pushed the lower pole of the kidney and ureter inward and is very probably retroperitoneal.

Blood Examination.—Hemoglobin 80 per cent.; leucocytes 11,050; erythrocytes 4,000,000; small lymphocytes 16; large lymphocytes 10; polynuclear neutrophiles 72; eosinophiles 2. (Laboratory, Georgia Baptist Hospital.)

X-ray Report No. 4440.—“No evidence of stones in the Genito-Urinary tract. Stomach normal in position and shows no filling defects. Peristaltic tone good. Colon injection shows filling defect of the transverse colon near the splenic flexure. This has the appearance of a malignancy, probably a carcinoma. Pyelogram shows no filling defects of kidney calyces. Kidneys normal in position.”

(Signed) J. W. Landham, Radiologist,
Georgia Baptist Hospital.

Operation, May 10, 1926.—Ethylene anesthesia.—Field of operation prepared with iodine and alcohol in the usual way. Right rectus incision, outer part of rectus muscle retracted inward. On reaching the peritoneum, it was pushed inward and the mass found to be extraperitoneal. It had a fairly well-defined capsule and easily separated from the surrounding tissues. There was no well-defined point of origin, but its main blood supply appeared to arise from the pelvic surface of the iliocostalis muscle. In fact these vessels were about all that required ligation, hot packs sufficing for the oozing in the rest of the area. The peritoneum was then opened and the appendix removed. No evidence of metastasis was observed in the abdominal cavity. The abdomen was closed in layers without drainage.

Pathological Report.—“Specimen appendix—5 cm. by 6 mm. Walls show slight fibrosis, mucosa swollen, with evidence of subacute inflammation. Specimen tumor—20 by 15 by 12 cm. Hard and fibrous in character. Gross appearance suggests sarcoma. Microscopic Diagnosis—Spindle Cell Sarcoma.”

(Signed) Geo. F. Klugh, M.D., Pathologist.

Patient left the hospital on May 20, 1926 and had a speedy convalescence. For some months following this operation her health was good and she resumed her school teaching in the fall of 1926. About the first of 1927 she noticed a return of the tumor in her right iliac region. She reported to Dr. M. B. Allen, who gave her a series of X-ray treatments, which held the growth in check for

a time, but it gradually increased in size until it was approaching its former size. It was thought best to remove it surgically again and then refer her for more X-ray therapy. She was admitted to the Georgia Baptist Hospital a second time as history No. 20688 on April 28, 1927. There was no apparent change in her general physical condition and her blood count, urinalysis and blood-pressure were practically the same as on her previous admission.

On April 29, 1927, under nitrous oxide anesthesia, an oblique incision 6 inches in length, 1 inch above the iliac crest and parallel to Poupart's ligament was made down to the tumor. The peritoneum was carefully pushed inward and the tumor had a rather poorly defined capsule and extended retroperitoneally behind the caecum and as high as the inferior pole of the right kidney. The retroperitoneal fat appeared opalescent and had glove-finger-like projections that extended so near the right ureter that it was impossible to remove all of it.

The larger rounded tumor mass was firmly attached to the iliocostalis muscle at the same site as the original tumor. The wound was closed and primary union was secured. The pathological report is as follows:

"Tumor, gross 8 by 6 by 6 cm. Recurrent Sarcoma.

Diagnosis—Myxo-Sarcoma."

(Signed) Geo. F. Klugh M.D., Pathologist.

Realizing that further surgical removal was impossible without damage to the right ureter, she was referred to the Albert Steiner Clinic of Grady Hospital for deep X-ray therapy. She was admitted on May 25, 1927, and the following progress notes taken from her chart will show the progress of her condition for the next three years. However, for the exact dosage and method of administration I shall refer you to Dr. Fike, Radiologist to Steiner Clinic.

May 25, 1927.—Abdomen brown from former X-ray treatment by Dr. M. B. Allen. One old right rectus scar and one recent right iliac scar with slight induration and tenderness from the pelvis to lower pole of right kidney. First series deep therapy given.

August 26, 1927.—Second series.

October 15, 1927.—"There is a slight sense of increased resistance in the right lower quadrant just above Poupart's ligament. No nodulation. Higher up in the line of the right rectus scar just lateral to the umbilicus is a small tender area which, felt through the rather thick pad of fat as an irregular lump, could easily be scar tissue in the rectus sheath."

(Signed) Dr. Fike.

March 10, 1928.—"Vague mass in right lower quadrant which seems to be somewhat tender. States that she had some pain for few minutes a week or two ago."

(Signed) Dr. Fike.

April 21, 1928.—No change. Another cycle of X-ray.

June 28, 1928.—"Abdomen seems much smaller and softer than on previous examination."

(Signed) Dr. Fike.

August 2, 1928.—"The small mass above Poupart's ligament on the right is more readily outlined and apparently somewhat smaller."

(Signed) Dr. Fike.

October 20, 1928.—Small mass felt just medial to the crest of the ilium. Patient looks and feels fine.

February 11, 1929.—Mass still 2 in. in diameter. To have X-ray from post part.

August 10, 1929.—Mass apparently same size. No pain or tenderness.

September 28, 1929.—Movable hard mass 2 in. in diameter in right pelvis. Some frequency of urination.

August 8, 1930.—Patient admitted to Steiner Clinic for removal of sarcoma mass. General condition good. Blood-pressure 106/58. Lungs clear. X-ray shows no evidence of metastasis in lungs. Blood: Red blood cells 3,350,000; hemoglobin 68 per cent.; white blood cells 7,400; polymorphonuclears 74 per cent.; large lymphocytes 4; small lymphocytes 17; transitionals 5. Urine: Faint trace of albumin, otherwise normal.

Operation, August 9, 1930.—With the assistance of Doctors Stewart and Wood of the surgical staff of the Steiner Clinic, we operated under nitrous oxide-ether anesthesia. The entire operation was done with the "electrical unit" installed by the American College of Surgeons for the experimental research in the control of cancer. The iliac scar was resected, including a pad of fat down to the muscles. These were divided by the cutting electric knife in "medium" position and the tumor mass resected deep into the substance of the iliacus muscle. The tumor was adhered to the peritoneum which in turn was adhered to the caecum and ascending colon. With the electric knife in "low" position these adhesions were carefully divided without damage to the intestinal wall. The retroperitoneal fatty tissue that appeared so malignant at the former operation three years previously appeared to be more fibrosed and contracted into scar tissue. All bleeding points were controlled by electrocoagulation and the muscular tissue from which it arose was caught up in large bites with hemostats and thoroughly coagulated. Two soft rubber drains were left in the extremities of the incision for forty-eight hours. Healing was by first intention and she was discharged from the hospital August 23, 1930.

The *pathological report* on the tissue removed follows:

"Specimen: Two masses from right iliac muscle. One mass 4 cm. long by 2½ wide and soft and encapsulated. Surrounded by normal appearing fatty tissue with some portions of muscle. Cross section shows a very gelatinous appearance of almost liquid consistency. The other mass is more solid, 2½ cm. in diameter and more rounded, with some fat and muscle. The cut surface is white and translucent and the section floats in solution.

"Microscopical Diagnosis. Sections show a mixture of various structures. There is a preponderance of somewhat atypical fatty tissue with cells of all sizes. There are scattered cells in dense stroma which cells are large and hyperchromatic. (Fig. 2.) Other areas show marked edema while in other portions the appearance is myxomatous with large sheets of basophilic material with small capillaries and numerous lymphocytes. (Fig. 3.) Vascularity is quite abundant throughout.

"No areas are very cellular and there is no necrosis, hemorrhage or infection.

"Diagnosis: Myxo-lipo-sarcoma; apparently of very low grade malignancy, the tendency to recur rather than to metastasize being more likely."

(Signed) Everett L. Bishop, M.D.
Physician in charge of Laboratory.

The patient looks well, has her normal weight and has resumed her teaching. She still reports to the Steiner Clinic for observation and occasional cycles of deep X-ray therapy to prevent a return of the growth. On her last visit, November 15, 1930, there was no evidence of a return.

The principal reasons for reporting this case are:

1. The rarity of myxoliposarcoma.
2. The persistence with which it recurs, and the marked influence of deep X-ray therapy in retarding the growth of a tumor, regarded as very largely radioresistant.
3. To compare the result of excision by ordinary surgical procedures with that of the radio-frequency excision with electro-coagulation of all bleeding points and of the area of muscle from which the tumor arose.

GAS BACILLUS SEPTICEMIA

By JACK C. NORRIS

Assistant Professor Pathology, Emory University

AND

HEYWARD S. PHILLIPS

Resident in Surgery, Grady Hospital, Atlanta, Georgia

THE gas bacillus of Welch and its allied group of disease producers are of increasing etiological importance in medicine and surgery. This paper deals with the organism of Welch alone in which its disastrous presence and destructive influence are studied in the report of a recent surgical patient at Grady Hospital—Emory Division.

The organism *B. aerogenes capsulatus* was discovered by Welch¹ in 1891. It was later described in detail by Welch and Nuttall.^{2, 3} It is believed that this organism is the same as *B. perfringens*, *B. emphysematis*, and *B. phlegmone emphysematosae*. The bacillus measures from 0.8 to 1.2 microns in diameter and 2 to 6 microns in length. It has square-cut ends and may occur either singly or in pairs. Spores may be formed. Absence of oxygen is necessary for growth. In a gram stain the violet color is retained. In cultures it grows best upon blood-agar or serum plates to which carbohydrate is added. The colonies are round, semi-translucent, and have very little color. On blood-agar plates it is noted that marked hemolysis occurs. In our laboratory we use as routine the cultural technic as described by Norris⁴ in Boland's⁵ article on "Gas Gangrene in Fractures." Considerable attention is paid in this technic of culture to the early appearance of gas sufficient to bubble and pass through 1.5 centimeters of sterile liquid petrolatum. Later, rabbit inoculations and culture studies confirm the identity of the organism.

The organism in the tissues produces hemolysins, thermostable toxins, gaseous elements, histamine bodies and butyric acid.

The bacillus is a common pathogen for man and animal. Most often it is associated with wounds that are made by dirty instru-

ments or in injuries which have become contaminated with earth. It is commonly found in the intestines of man or animal. Deep wounds or wounds with considerable necrosis predispose and enhance its growth. Not infrequently it is associated in wounds in which the prominent symptoms are tetanic.

As to the occurrence of gas bacillus infections, Boland⁶ reports the infection in 19 per cent. of a series of compound fractures occurring in seven years. Smith⁷ reports an infection following tonsillectomy. Shearer⁸ reports an infection with the germ involving the abdominal wall following appendectomy. In all of the cases above, however, gas formation and crepitus were noted in the tissues externally.

The case presented in this paper is most unusual because of the septicemic effects and the absence of gas in general, and also because of the evidence of profound toxemia noted in the tissues at the necropsy.

L. W., colored male laborer, aged 38 years, was admitted to the hospital on September 11, 1930, and died at 11:15 P.M. on the day following. He was complaining of being "ruptured." He had been suffering from transient hernial obstruction for a period of six years. At the time of admission the gut had been unreduced for over thirty hours. He was suffering severe pain and was vomiting frequently. The facies was hippocratic. His lips were dry. His pulse was rapid and almost imperceptible. His fever recorded 101.5°. His abdomen was rigid and tender. The blood count revealed 84 per cent. polymorphonuclears, 16 per cent. lymphocytes, with a total white cell count of 11,000 per cubic millimeter. After stimulation and fluid infusion with glucose and saline he was operated upon under novocain anesthesia. Upon reducing the hernial contents it was noted that 2 inches of the small intestines were gangrenous. To facilitate the procedure and aid the patient in withstanding the shock, the gangrenous loop of gut was pulled outward and the healthy gut surrounding sewed to the abdominal wall; thus establishing functional enterostomy. The extreme toxemia of the patient was more than that usually observed in these cases. There was no satisfactory reaction after the operation. He died eleven hours later.

AUTOPSY ON L. W., SEPTEMBER 12, 1930, NO. 41516—A-30-120—BY DOCTOR NORRIS

General Appearance.—The body is that of a well-developed, well-nourished colored male about thirty-eight years of age, measuring 153 centimeters in length and weighing 145 pounds. Rigor mortis is present, also posterior lividity. No edema. Scars: Recent surgical wound in the left inguinal region which measures 11 centimeters. Pupils: Contracted; conjunctive hemorrhagic.

Peritoneal Cavity.—There is a small amount of blood. No evidence of peritonitis is seen. Ileostomy is formed in the ileum about 27 centimeters

FIG. 1.



Lungs from case of gas bacillus septicemia.

ments or in injuries which have become contaminated with earth. It is commonly found in the intestines of man or animal. Deep wounds or wounds with considerable necrosis predispose and enhance its growth. Not infrequently it is associated in wounds in which the prominent symptoms are tetanic.

As to the occurrence of gas bacillus infections, Boland⁶ reports the infection in 19 per cent. of a series of compound fractures occurring in seven years. Smith⁷ reports an infection following tonsillectomy. Shearer⁸ reports an infection with the germ involving the abdominal wall following appendectomy. In all of the cases above, however, gas formation and crepitus were noted in the tissues externally.

The case presented in this paper is most unusual because of the septicemic effects and the absence of gas in general, and also because of the evidence of profound toxemia noted in the tissues at the necropsy.

L. W., colored male laborer, aged 38 years, was admitted to the hospital on September 11, 1930, and died at 11:15 P.M. on the day following. He was complaining of being "ruptured." He had been suffering from transient hernial obstruction for a period of six years. At the time of admission the gut had been unreduced for over thirty hours. He was suffering severe pain and was vomiting frequently. The facies was hippocratic. His lips were dry. His pulse was rapid and almost imperceptible. His fever recorded 101.5°. His abdomen was rigid and tender. The blood count revealed 84 per cent. polymorphonuclears, 16 per cent. lymphocytes, with a total white cell count of 11,000 per cubic millimeter. After stimulation and fluid infusion with glucose and saline he was operated upon under novocain anesthesia. Upon reducing the hernial contents it was noted that 2 inches of the small intestines were gangrenous. To facilitate the procedure and aid the patient in withstanding the shock, the gangrenous loop of gut was pulled outward and the healthy gut surrounding sewed to the abdominal wall; thus establishing functional enterostomy. The extreme toxemia of the patient was more than that usually observed in these cases. There was no satisfactory reaction after the operation. He died eleven hours later.

AUTOPSY ON L. W., SEPTEMBER 12, 1930, NO. 41510—A-30-120—BY DOCTOR NORRIS

General Appearance.—The body is that of a well-developed, well-nourished colored male about thirty-eight years of age, measuring 153 centimeters in length and weighing 145 pounds. Rigor mortis is present, also posterior lividity. No edema. Scars: Recent surgical wound in the left inguinal region which measures 11 centimeters. Pupils: Contracted; conjunctive hemorrhagic.

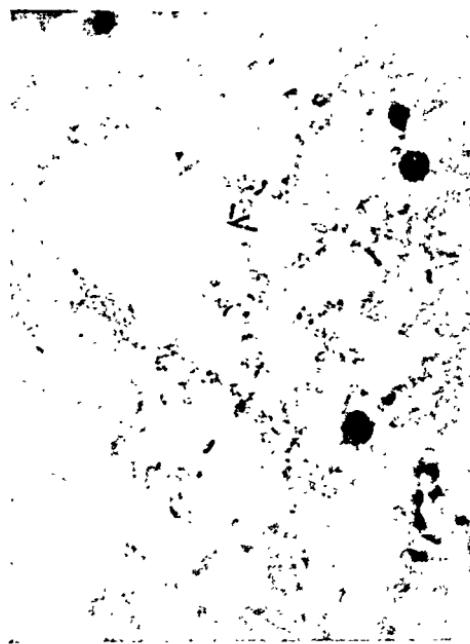
Peritoneal Cavity.—There is a small amount of blood. No evidence of peritonitis is seen. Ileostomy is formed in the ileum about 27 centimeters

FIG. 1.



Lungs from case of gas bacillus septicemia.

FIG. 2.



Illustrating the bacilli within the tissues.

FIG. 3.



Section from lung illustrating the necrosis and the remarkable distention of the alveoli with gas, one of which also has edematous fluid within it.

from the ileocecal junction. No evidence of intestinal obstruction noted. Appendix is in the lateral quadrant and measures about 9 centimeters. No disease. Diaphragm reaches the fifth rib on the right and the fifth on the left.

Pleural Cavities.—Contain no fluid except small amount of bloody exudate. No adhesions noted. *Lungs:* Left lung weighs 470 grams. Right weighs 600 grams. The lungs are remarkably congested and the cut surface shows the vessels filled with impacted blood. The tissue is bluish-red in color except for the upper margins which have a normal grayish tinge. In the areas of congestion there is some resistance to the feel. The blood-cells in the pleural exudate, and the blood which exudes from the lung alveoli, show a diffuse and marked hemolysis. Upon laying the lungs with cut surfaces upward upon the table, it was noted that from several areas small gas bubbles made their appearance. There are numerous petechiae over the pleural surfaces.

Pericardial Cavity.—No increase in fluid. No adhesions present. The fluid is slightly red.

Heart.—Weighs 320 grams. There are many hemorrhagic petechiae about the coronary terminal vessels. This is a very pronounced finding. The petechial hemorrhages are large, irregular and fan-shaped and appear unusual. Musculature is very soft and flabby. Valve measurements are: pulmonary, 6 centimeters; tricuspid, 13 centimeters; mitral, 10 centimeters; aortic, 6 centimeters. The mitral and aortic valves are red and fibrous. No ante-mortem pulmonary clot is noted. Aorta is smooth, expansile and glistening.

Liver.—Congested and very flabby. Also pale and soft. It weighs 1,200 grams.

Gall-bladder.—Filled with bile.

Spleen.—Is soft and flabby and weighs 65 grams.

Pancreas.—Is soft and flabby and weighs 60 grams.

Kidneys.—The left kidney weighs 140 grams; the right weighs 150 grams. Both kidneys, except for a mild congestion, are negative. Vessels show hemolysis of blood cells.

Glandular.—Negative.

Genitalia.—Negative.

Gastro-intestinal Tract.—Ileostomy with a gut emptying externally. The wound is uninfected. The gut shows gangrene at the incision.

Anatomical Diagnosis.—Septicemia. Toxic myocarditis; toxic valvulitis. Operative ileostomy. Toxic splenitis, hepatitis, nephritis.

Blood culture from heart showed *B. welchi* and streptococci. Culture and smears from coronaries showed *B. welchi*. Culture from lung infarcts showed *B. welchi*.

The summary of the necropsy based upon the organism's presence in the circulation and within the coronary vessels and the lungs, encourages me (J. C. N.) to conclude that this man was suffering from a severe septicemia due to the gas bacillus. His rapid pulse, temperature and profound symptoms support this diagnosis.

While it is scientifically correct to diagnose *B. welchi* infections when gas and crepitus are noted, we feel that surgeons perhaps are overlooking these types of infections in many of their fulminant

cases with gangrenous gut, as in hernia, obstruction, *etc.*; and it is suggested that a prophylaxis of intravenous mixed antiserum be given routinely in these cases so as to protect the patient from the disease results of gas bacilli, *B. tetani* and streptococci. This suggestion is based upon findings in this case and upon the following facts:

1. The constant presence of these organisms in the intestinal tract.
2. Constant association and easy growth of the germs in gangrenous tissues.
3. The easy access of the organism into the circulation from gangrenous tissue.

SUMMARY (Figs. 1, 2, and 3)

1. The characteristics of the *Bacillus welchi* are briefly reviewed.
2. A case of septicemia due to this organism is presented.
3. A surgical patient suffering with intestinal gangrene who has evidence of pronounced toxemia, fever, rapid pulse and leukocytosis should be observed closely for gas bacillus infection and treated accordingly.

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I. REFLEX HICCOUGH II. PARTIAL LOBECTOMY FOR
CHRONIC EMPYEMA OF THE PLEURA III. THE
TWO-STAGE OPERATION FOR ABSCESS
OF THE LUNG

By D. C. ELKIN, M.D.

Emory University, Atlanta, Georgia

REFLEX HICCOUGH

HICCOUGH from direct irritation of the diaphragm, as seen in subphrenic or liver abscess, or from irritation of the phrenic nerve by mediastinal inflammation or neoplasms, is of fairly frequent occurrence. The diaphragm may be indirectly influenced to contract by reflexes having their origin in the gastro-intestinal tract (carcinoma of the stomach, cholecystitis), and from certain toxemias (alcoholism, peritonitis, uremia).

The following case illustrates a direct reflex hiccough from irritation arising in the region of the trapezius muscle, and its cure by temporary interruption of the impulses to the diaphragm by crushing the phrenic nerve.

J. H., No. 42110, a negro man of twenty-eight, entered the Emory University division of the Grady Hospital on October 20, 1930, because of persistent hiccoughs of four days' duration. Eight days previously he had been stabbed in the left trapezius region, and the wound, which was superficial, was sutured and he returned to work.

On October 16, four days after receiving the stab wound, he began to hiccough, and this continued constantly until his entrance to the hospital. During the four days of hiccoughing he had not slept and had eaten very little.

On examination he was found to be irrational, drowsy, and apparently quite sick, with a temperature of 101°, pulse 100. He was hiccoughing continually. The wound in the posterior portion of his left trapezius muscle was fluctuant. It was opened and about 15 cubic centimeters of pus evacuated. Exploration of the wound showed that it was confined to the subcutaneous tissues and the muscle, and did not extend into the anterior part of the neck nor into the mediastinum.

Fluoroscopic examination of the chest showed paroxysmal contractions of both sides of the diaphragm about ten times per minute. He was given large doses of luminal, bromides, chloral, sodium amytol and morphine for three days without effect.

On November 23, seven days after the onset of the hiccough, the left

phrenic nerve was exposed in the neck under local anesthesia and crushed in three places. Within thirty minutes the hiccup ceased, but returned for twenty minutes the next day. Following that there was no return and his recovery was rapid and uneventful. Fluoroscopic examination after crushing the nerve showed that the left diaphragm was elevated and immobile.

Fig. 1 illustrates the connections of the phrenic nerve, which arises from the third, fourth and fifth cervical nerves. The sensory supply to the trapezius muscle and the skin over it arise from the same segments. Fig. 2 shows the reflex arc by which impulses pass from the trapezius muscle to the diaphragm.

PARTIAL LOBECTOMY FOR CHRONIC EMPYEMA OF THE PLEURA

H. G., No. 8317, a white man of twenty-one, entered the University Hospital November 5, 1930, because of a chronic discharging sinus from the back of his left chest.

In 1918 he had empyema of the left pleura following pneumonia. Rib resection with open drainage was done at that time, but the wound never healed except for short intervals. Since the first operation, twelve subsequent ones had been performed in an attempt to secure adequate drainage and obliteration of the cavity.

Physical examination showed a well-developed but somewhat undernourished man. His temperature, pulse and blood counts were normal. His physical examination was entirely normal except for a small discharging sinus in the left ninth interspace posteriorly.

Roentgenogram of the chest was normal (Fig. 3) and it was at first thought that the sinus was due to a chronic osteomyelitis of rib, although this could not be demonstrated in the film.

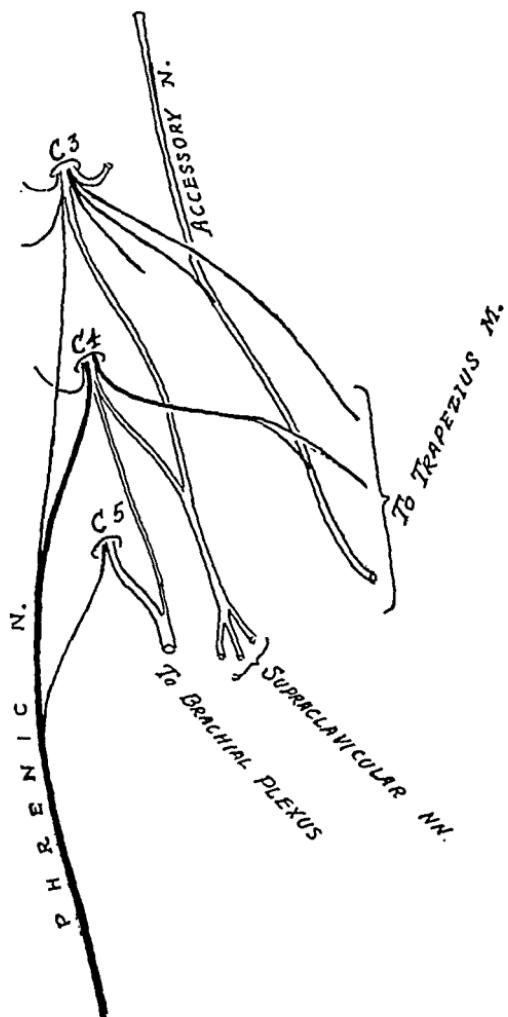
A subsequent roentgenogram, made after injecting the sinus with lipiodol, revealed a cavity about 6 centimeters in diameter and with finger-like projections into the substance of the lung (Fig. 4).

Operation was performed on November 10, 1930. The sinus leading into the cavity was enlarged by removal of the regenerated rib, and the cavity exposed. The lining membrane was about 1 centimeter thick and so adherent to the lung tissue that it could not be stripped off, and pockets which dipped into the lung tissue likewise made decortication impossible. The cavity was therefore removed in its entirety by cutting through healthy lung tissue outside the lining membrane (Fig. 5). The lung tissue was clamped and ligated and packed to control bleeding. The packing was removed at the end of five days and irrigations of the now healthy cavity were begun. There was no evidence of a bronchial fistula, and the cavity was rapidly expanded by forced expiration by means of blow bottles.

Since the cavity lay directly on the left diaphragm, it was thought that paralysis of this muscle, and its subsequent rise into the chest would further obliterate the cavity. On November 25, 1930, the left phrenic nerve was exposed in the neck and crushed in three places. Fluoroscopic examination and roentgenogram showed the diaphragm paralyzed and elevated (Fig. 6).

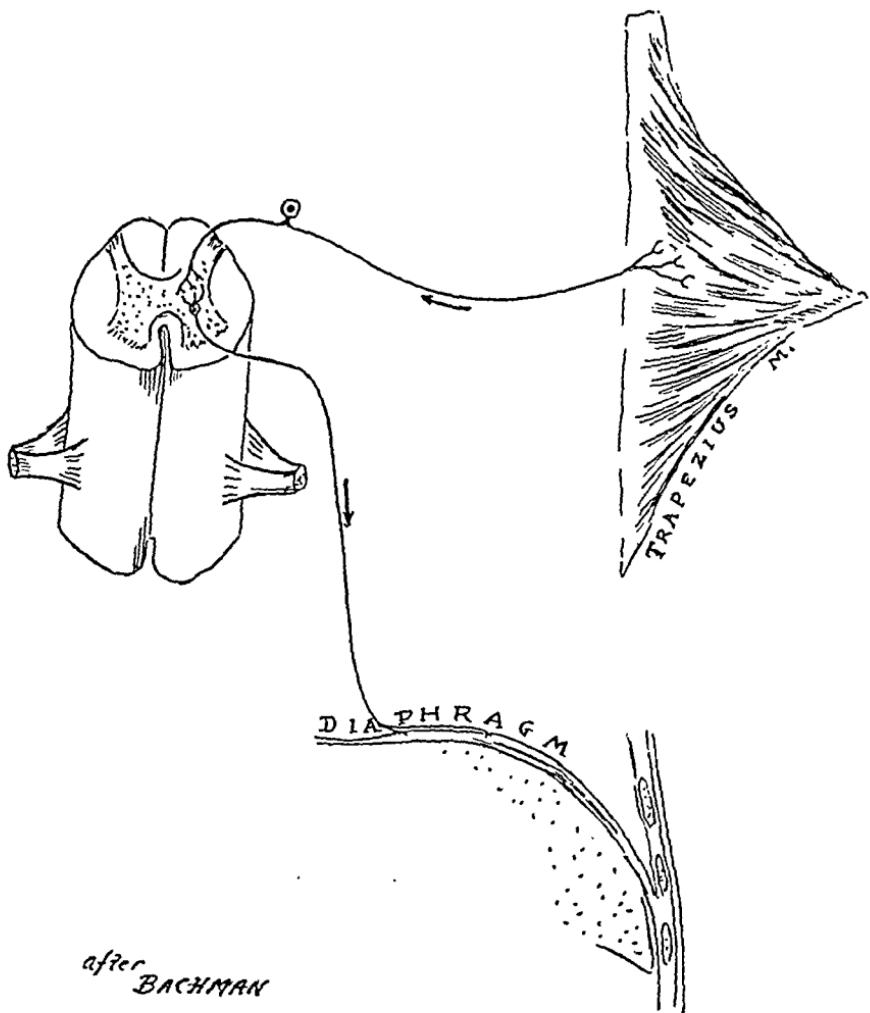
The wound was irrigated every three hours with Dakin's solution and forced expiration to expand the lung was done hourly. The cavity gradually decreased in size and is now practically obliterated.

Fig. 1.



Connections of phrenic nerve.

FIG. 2.



after
BACHMAN

The reflex arc connecting the trapezius muscle and the diaphragm.

FIG. 3.



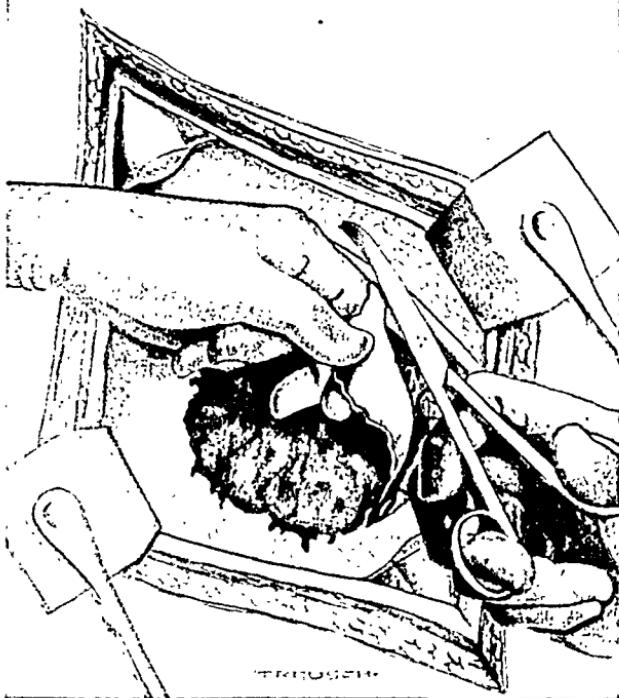
Roentgenogram of chest. The only abnormal finding is the absence of the tenth rib.

FIG. 4.



Roentgenogram after injection of the sinus with lipiodol. Note the numerous pockets from the cavity into the lung.

FIG. 5.



Method of removing the cavity wall. The pockets into the lung necessitated removal of considerable lung tissue.

FIG. 6.



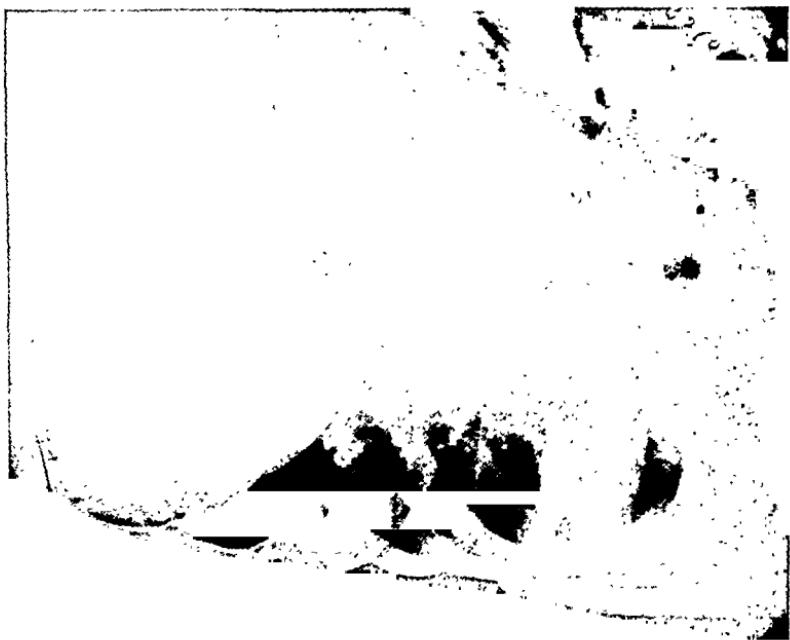
Roentgenogram after crushing the phrenic nerve. The left diaphragm is elevated.

FIG. 7.



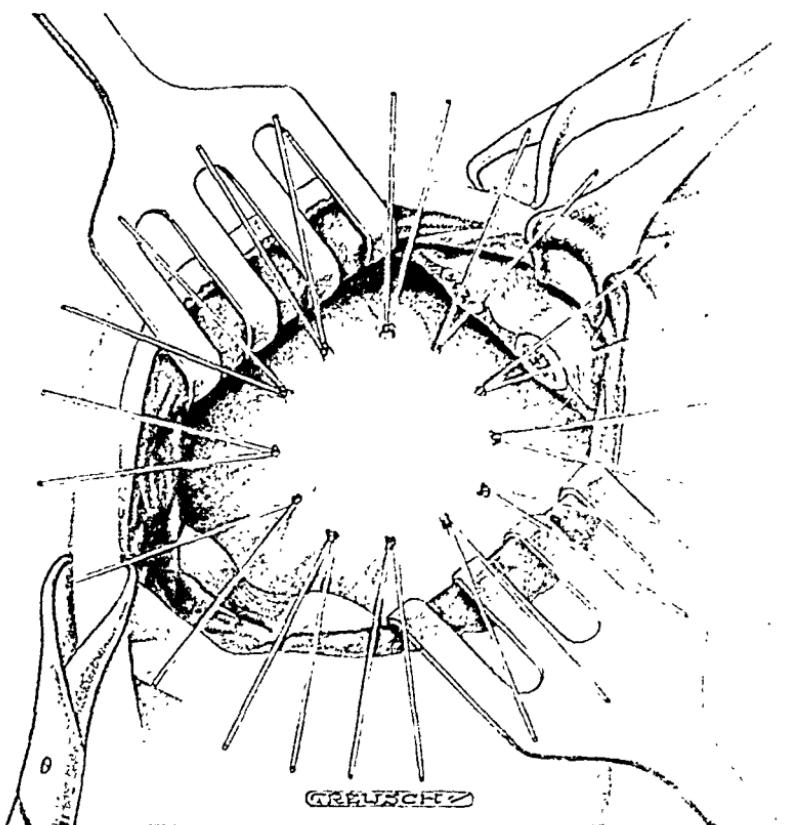
Antero-posterior roentgenogram of the chest. There is a large abscess cavity with a fluid level in the right upper lobe.

FIG. 8.



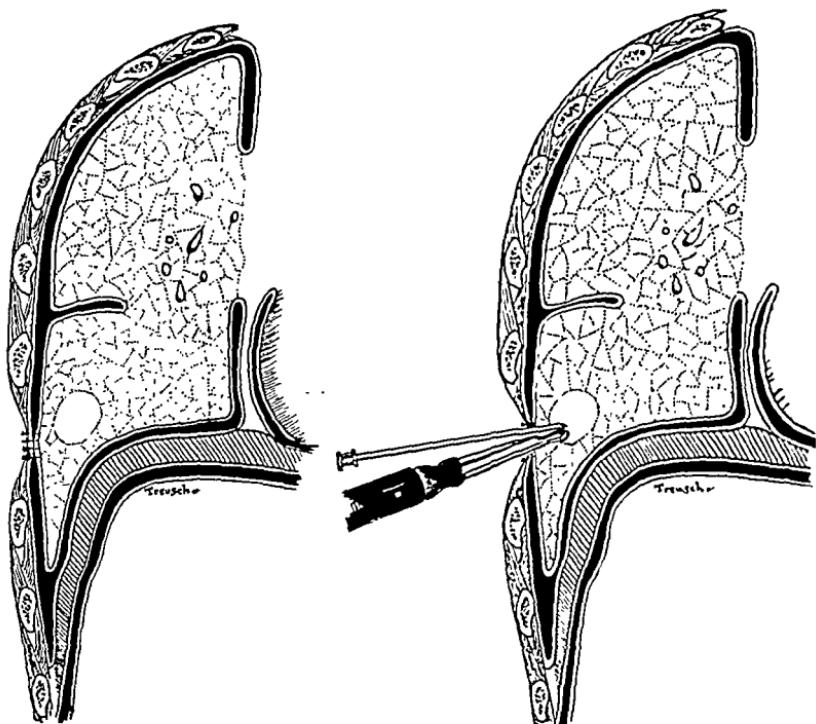
Same as Figure 7 in the right oblique position. The cavity is seen posteriorly against the ribs and beneath the scapula.

FIG. 9.



The first stage operation. The sutures which have passed through both pleural surfaces are left long and tied over gauze.

FIG. 10.



The pleural surfaces are stitched and packed with gauze. The cautery follows the needle into the abscess.

FIG. 11.



Roentgenogram of chest three months after drainage of the abscess.

Comment.—Partial lobectomy for the cure of a chronic empyema cavity seems a radical and dangerous procedure, and should be done only where other less radical methods fail to cure. In this instance the disease had been present for twelve years, the cavity lining was thick and fibrous and thirteen operations had failed to effect a cure. In such a case complete removal of the chronically infected pleura is essential, and if pockets project into the lung the only method of removal is by partial lobectomy.

THE TWO-STAGE OPERATION FOR ABSCESS OF THE LUNG

B. A., No. 48297, a man of fifty, entered the University Hospital on January 7, 1930, suffering from bronchopneumonia. He was exceedingly sick and at times it was thought that he would not recover. The pneumonia subsided gradually and on January 28 his temperature was normal, and remained so for one week. On February 3 his temperature began to rise to 102° in the afternoon. At about this time he began to cough up large quantities of foul, thick, yellow sputum. A roentgenogram showed a large abscess cavity in the right upper lobe. There was a definite fluid level, and the lateral film showed the cavity lying near the posterior surface of the lung (Figs. 7 and 8).

Postural drainage was instituted for three weeks, during which time there was no improvement in temperature, expectoration, or in the general condition of the patient. A second roentgenogram showed no decrease in the size of the cavity, and accordingly operation for external drainage was carried out on February 24, 1930.

Under local anesthesia, portions of the fifth, sixth, and seventh ribs were subperiosteally resected on the right side posteriorly. This exposed the area of the abscess as located by the roentgenogram. When the parietal pleura was exposed it was found that it was not adherent to the underlying visceral pleura. The two pleural surfaces were therefore stitched together with interrupted sutures of fine catgut. The sutures were left long and tied over gauze which would further tend to form adhesions between the pleural surfaces (Fig. 9).

Three days later the gauze was removed from the wound and the second stage in the drainage of the abscess carried out. After the pleura was infiltrated with novocaine, a large aspirating needle was passed through the adherent pleural surfaces into the abscess. The needle was left in place and its edge followed through the lung into the abscess with a cautery (Fig. 10). When the cautery reached the abscess the opening was further enlarged and the whole posterior wall of the cavity burned away in order to secure greater collapse of the cavity. Two soft rubber drains were placed in the cavity and sutured to the skin.

Following this external drainage the temperature rapidly dropped to normal and expectoration ceased. Within four weeks the bronchial fistula healed and in six weeks the external opening had closed. On May 15, ten weeks after the operation, the skin wound was healed and the roentgenogram of the chest showed no evidence of abscess or lung infection. At the present time the patient is in good condition with no evidence of infection (Fig. 11).

Comment.—Recovery in abscess of the lung usually takes place in one of three ways: (1) by drainage through the bronchus, in which bronchoscopic aspiration may be of value; (2) by operative external drainage; and (3) by rupturing into the pleura and by drainage of the resulting empyema.

In every instance, as in the one here reported, postural drainage should be tried and many cases respond. If no improvement takes place within three or four weeks, external drainage is indicated; otherwise a chronic, thick-walled abscess will result, a suppuration throughout the lung may occur, or the abscess may rupture into the pleura.

In practically every case of external drainage the operation is best done in two stages in order to prevent the possibility of empyema. Aspiration before operation is dangerous because pus may enter the pleural cavity when the needle is withdrawn or may infect the chest wall.

The use of the cautery in opening into the cavity is important in preventing hemorrhage and in sealing off healthy lung tissue.

COMPLETE PROLAPSE OF THE RECTUM

By W. E. PERSON, M.D.
Atlanta, Georgia

COMPLETE prolapse of the rectum is a relatively rare anorectal disease. There have been ten cases admitted to the Emory University division of the Grady Hospital the past nine years. All have been in the colored race.

Complete prolapse of the rectum is a condition in which all the coats of this viscus slide downward, and if not corrected a conical mass with a slit-like opening protrudes through the anus. Much confusion has existed as to its nature. One view is that the rectum only is affected. The other view is that the rectum is involved secondarily, the gut being pressed downward and out, in fact, a hernia.

Moschowitz was the first American author to believe that complete prolapse was a sliding hernia, and caused like all hernias by anatomical weakness of the abdominal wall and intra-abdominal pressure.

Method of Production.—Whenever a vessel or viscus leaves the abdomen it must perforate the transversalis fascia. The rectum perforates the pelvic fascia (a continuation of the transversalis fascia) in the pelvis. Normally the fascia is firmly united to the rectum. In some cases this union is weak, and unable to sustain the weight of the intestines. This permits a deepening of the cul-de-sac. Increased intra-abdominal pressure from any cause as hard manual labor, coughing, straining at stool, urinary obstruction, etc., is a potent factor.

The next stage is a bulging of the anterior wall of the rectum from the weight of the small intestines, which gradually becomes more pronounced until the posterior wall of the rectum is reached. Here it is held for a time by its ligamentous attachment and the sacrococcygeal curve. Finally the supports weaken and the rectum slides downward to the firmly fixed anal canal. Prolonged pressure stretches the levators and sphincter. The latter becomes paralyzed

by the pressure. As the anal canal is fixed it does not take part in the prolapse, but the rectum continues to invaginate. Later a conical mass appears outside the anus.

Diagnosis.—Pain is not a prominent symptom, though the coccyx has been removed for coccydynia. Discomfort in the pelvis and sacral region is usually present. Incontinence, protrusion and bleeding are the most troublesome features. The rectum is inflamed and erosions are common, which often causes a muco-purulent bloody discharge. A secondary anemia is often severe. Disability is so pronounced that the patients have to change occupations or quit work.

Distinction must be made between the two types of rectal prolapse—the partial, or incomplete, and the complete. A thorough examination will easily solve the problem.

In the complete type the mass is somewhat constricted at the anus, getting larger at the middle and then tapering off to the conical extremity with a slit-like opening. This opening is nearer the posterior border than the anterior. On the anterior surface tympany and gurgling can be demonstrated. In early cases and after reduction impulse on coughing and bulging can be felt by digital examination. Moschowitz emphasizes another point in the diagnosis—that is, after reduction by pressure of the hand on the anterior wall of the rectum the prolapse cannot be reproduced. The sulcus between the anal canal and rectum is of diagnostic value in adults, but not so reliable in children.

Young children do have complete prolapse like adults, but care will have to be exercised in the differentiation between some cases of mucous membrane prolapse and the complete type.

The mucous membrane prolapse in children when recently extruded is of more uniform size, is smoother, the rugae are not quite so circular, and the opening is more centrally placed. The other diagnostic features of a hernia are absent.

A barium meal followed by an X-ray examination will demonstrate the small intestines outside the anus enclosed in the sac, which is the prolapsed rectum. It is essential that the prolapse be reproduced and that the picture be made in the standing position to get the best results (Fig. 1).

Operation.—The cure rests upon the same principles as in any

FIG. 1.



Skiagraph of barium meal in prolapse of rectum.

FIG. 2.



Barium filled intestines high in pelvis and not outside of the anus.

hernia. The sac must be extirpated or obliterated and the normal supports restored. The sac—in this instance the deep pelvic pouch—can only be obliterated. Moschowitz uses purse-string sutures for this closure. It is more convenient for me to suture from front to back (Fig. 1). The peritoneum should be sutured to the rectum and sigmoid. Care should be exercised to close snugly around the gut, but to avoid making any constriction. The bottom cannot be reached for suturing. However, no dead space will remain. If this portion is irritated, union will be prompt. The operation is easier in women than in men, the female pelvis being more capacious and the uterus can be used for traction. The only things to be avoided are the ureters and internal iliac vessels. The suturing should be carried up to the second sacral vertebra. It is well in women to catch the uterus in the sutures. Fig. 2 shows barium-filled intestines high in the pelvis and not outside of the anus.

Postoperative course.—No special postoperative treatment is needed, except no laxatives are given.

The relaxed sphincter begins to regain its tone as soon as the load is removed. At the time of operation the whole hand will usually enter freely; two weeks after, three fingers will be a tight fit, and six weeks postoperative one finger can be inserted easily and two fingers under pressure.

The ten cases were divided as to sex as follows: two females and eight males. Two of the males were children.

The ages were: women nineteen and twenty-seven, men twenty-four, twenty-seven, twenty-seven, forty, forty-three and fifty-four respectively. Both children were two years of age.

Comment.—The first case, a woman, aged nineteen, was admitted to the hospital for arthritis, bleeding from the rectum and a chronic purulent rectal discharge. When examined an abscess was in the posterior rectal wall near the anus, and there was a proliferative proctitis with ulceration. The sphincters were widely dilated and there was a relaxation of the whole rectum with slight prolapse. The abscess was drained. Later a plastic operation was done to narrow the outlet. At this time I did not comprehend the real diagnosis—a complete prolapse. I watched the development until a very large mass protruded, which took about six months. Then Moschowitz's procedure was advised but recurring attacks of arthri-

tis and fever of unknown origin postponed operation until ten months had elapsed after I had first seen her. At operation the cul-de-sac extended to the level of the external sphincter. Unfortunately she died the fourth day postoperative from lobar pneumonia.

The other female had previously been operated on for tubal disease and hemorrhoids. She was cured of the prolapse, but developed a rectal stricture six months after operation. This is not surprising as negro women are very prone to have this from any inflammation in or around the rectum.

The third case was a very interesting one, though unfortunately the result was death. This man, aged twenty-seven, was admitted to the hospital the first time for urinary retention caused by multiple strictures of the urethra. The first sign of urinary obstruction was fourteen months previous. Rectal bleeding and prolapse came several months later. The strictures were dilated and he was allowed to go home. He was soon readmitted for treatment of the prolapse. When a 26 sound could be passed operation was done. He did well for seventeen days, then he passed blood per rectum. He died suddenly on the eighteenth day postoperative. A limited autopsy was done. No signs of peritonitis or obstruction were present. The caecum, ascending and transverse colon were filled with blood. This was a puzzle to me. In an effort to demonstrate the barium in the small intestine outside the anus many X-ray exposures had been made. This was due to a misunderstanding of what was wanted, and unnecessary pictures were taken. Doctor Fike (radiologist to the Steiner Clinic) expressed the opinion that the hemorrhage was due to the X-ray. His views were confirmed by Bachem, Colwell and Ross.

Another case who had several needless exposures for the same reason showed at operation a caecum and ascending colon filled with blood. The bladder bled after the operation and I do not believe the bladder was injured by any operative procedure. This man made an uneventful recovery.

One had an acute prolapse due to hard work and coughing. Several tried to reduce it, but were unable to do so. He was admitted to the hospital and the reduction made with considerable difficulty under anesthesia. He died from pulmonary tuberculosis. Operation was not advisable.

There has been one known case to recur. This took place about two years postoperative.

SUMMARY

1. There were three deaths in the series of ten cases. Two were postoperative.
2. Complete prolapse of the rectum is a hernia, as shown by the X-ray.
3. It is cured by the same general principles as are other hernias.

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Remarks on Recent Progress and Important Developments in Medicine, Obstetrics, Pediatrics, and Surgery*

MEDICAL TREND

By HENRY W. CATTELL, A.M., M.D.

Thrice Editor of INTERNATIONAL CLINICS (1900-1903; 1910-1916; and 1922-)

THE WORLD'S UNREST

The zealous but unenlightened social reformer and the ignorant politician are alike apt to see conspiracies of the deepest dye behind the operation of those economic laws which make it impossible to extract a quart out of a pint pot.—JEANS: *The Mysterious Universe*, 1930.

IN THE article on the Progress of Medicine during the year 1912, I quoted the words spoken by Lord Roseberry at the Congress of Universities of the British Empire held at London two years before the outbreak of the World War, and which are as follows:

Is not the whole world in the throes of a travail to produce something new, something perhaps better than we have ever known, which it may take long to perfect or to achieve, but which, at any rate, means a new evolution?

According to Roger W. Babson, the noted economist and statistician, business depressions are caused by dissipation, dishonesty, and a general collapse of moral character, while, on the other hand, they are cured by a moral awakening in which the people must be "conditioned," as the psychologists say, in right ways of working and living on all three sides of the triangle of physical, mental, and spiritual values.

Kipling writes (1930):

* This short review covers the period from February 1, 1930, to February 9, 1931, but it is to be remembered in the reading thereof that many topics not touched upon have recently been gone over by the insertion of original articles covering these grounds during the publication of the fortieth series of the INTERNATIONAL CLINICS, that they will be found in the present issue, or that they are scheduled to appear in future volumes.—EDITOR.

..... But our hour
Comes not by staves or swords
So much as subtly comes through power
Of small corroding words.

With these thoughts in mind contained in the quoted opinions of Jeans, Roseberry, Babson, and Kipling—and many others in a similar vein might be given—and knowing full well that there are certain fundamental laws—as unchangeable as those of the Medes and Persians until they passed away—of economics, ethics, and hygiene which may not be broken without paying the penalty to the individual or to the State, I am asking myself, both as an individual and as but one part of the 122,775,046 of the population of the continental United States and of the over two billion of persons of the world, what can I do, in my feeble way, to be of service other than to follow the dicta of doing the day's work, as it unfolds itself, in the best possible manner, and then within one's own limitations let the morrow take care of itself?

THE FUTURE OF THE MEDICAL PROFESSION AS A WHOLE

The trend towards state medicine is steadily progressing, and in my opinion, sure to become an actuality in some form or other, and this, too, in the not very distant future, and the beehive of industry must, in some manner or other, be taken care of by the medical profession working as a unit. Let us hope and trust that our own leaders may prove themselves good men, and true to their responsibilities, and take proper care of the throes of labor in producing something new, something better, in this new evolution that is so rapidly being perfected. In the meantime, should not each individual physician endeavor to the best of his ability to weigh and to act on the evidence produced by the zealous, but unenlightened, social reformer, working in the open and the ever-present pot-house politician working under cover, and then to put his or her own house in order for the strenuous days of struggle that are still to come?

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THE WORLD'S UNREST

The zealous but unenlightened social reformer and the ignorant politician are alike apt to see conspiracies of the deepest dye behind the operation of those economic laws which make it impossible to extract a quart out of a pint pot.—JEANS: *The Mysterious Universe*, 1930.

IN THE article on the Progress of Medicine during the year 1912, I quoted the words spoken by Lord Roseberry at the Congress of Universities of the British Empire held at London two years before the outbreak of the World War, and which are as follows:

Is not the whole world in the throes of a travail to produce something new, something perhaps better than we have ever known, which it may take long to perfect or to achieve, but which, at any rate, means a new evolution?

According to Roger W. Babson, the noted economist and statistician, business depressions are caused by dissipation, dishonesty, and a general collapse of moral character, while, on the other hand, they are cured by a moral awakening in which the people must be "conditioned," as the psychologists say, in right ways of working and living on all three sides of the triangle of physical, mental, and spiritual values.

Kipling writes (1930):

* This short review covers the period from February 1, 1930, to February 9, 1931, but it is to be remembered in the reading thereof that many topics not touched upon have recently been gone over by the insertion of original articles covering these grounds during the publication of the fortieth series of the INTERNATIONAL CLINICS, that they will be found in the present issue, or that they are scheduled to appear in future volumes.—EDITOR.

in the number of circulating antibodies, for immunity may persist after the disappearance of such antibodies. This type of immunity expresses itself as hypersensitivity which, with the non-bacterial antigens, may be harmful. But hypersensitivity to the bacterial antigens may, in some of its aspects, represent an acceleration of the local inflammatory reaction and, in this sense, possess defensive functions.

The protective functions of the body, as pointed out by Kyes, reside in large part in the cells of the reticulo-endothelial system—the histocytes of Maximow. Protective forces subsidiary to this system, such as opsonins which activate phagocytins, and bactericidal powers of the plasma, work interdependently with the reticulo-endothelial system.

The skin is far more than simply an integument—its significant properties of local resistance, according to Besredka, entitle it to be placed in the class of special organs. Since some organisms have specific virulence for the intestinal mucosa while others have specific virulence for the skin, it has been reasoned by Besredka that it is sufficient in each particular case to immunize only the susceptible tissue in order to prevent infection. The mechanism of the time-honored hot, wet dressing or poultice as a measure for localizing an inflammation is practically identical to that of Roentgen-rays and light rays in the power of both of them to stimulate the reticulo-endothelial system in the production of protective cells. Such a simple procedure as the intracutaneous injection of lactalbumen or broth filtrate or even water will produce a marked redistribution of protective cells in the body. This is brought about, according to Müller, by a stimulation of the sympathetic system, which in turn produces a peripheral vaso-dilation with corresponding splanchnic vaso-constriction. The injection of various proteins and sera, non-specific in nature, produces very beneficial results in a number of acute and chronic infections through a complicated systematic inflammatory reaction. "To mention only a few of the significant things which follow upon the injection of it—let us say—typhoid vaccine in moderate dose: There is a powerful reaction in the bone marrow, with temporary leucopenia followed by a considerable increase in circulating leukocytes; there is enhanced activity of the reticulo-endothelial system and an increase in blood platelets; there

PROGRESS IN MEDICINE, WITH SPECIAL REFERENCE TO DIAGNOSIS AND TREATMENT

By HENRY W. CATTELL, A.M., M.D.

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IMMUNITY

Immunity, which had its humble origin in the observation of the specificity of antibodies and which reached adolescence in the discovery of antitoxins, agglutinins and autohemolysins, has certainly advanced in years with the recent clinical applications of its ever-changing conceptions. The side-chain theory and similar pictorial conceptions are in danger of becoming obsolete and being replaced by the older conception which "favored the incorporation of some of the antigenic constituents in the antibody."

Professor Hans Zinsser,¹ in his recent talk before the New York Academy of Medicine on the subject of immunity, of which the following is a condensation, feels that the hunt has now broken into open country and that the hounds are in full cry again. The fundamental protective mechanism maintaining the integrity of the tissues against the entrance of foreign materials is displayed in the phenomenon of inflammation which is virtually an expression of natural immunity.

When a non-antigenic substance, such as dust, enters the body it is either removed or stored. When, on the other hand, an antigenic substance, such as one of the many proteins, gains entrance to the body there is a defense reaction leading to an artificial immunity. Each subsequent entrance of the antigen modifies the body's reaction to it. An infectious disease, *in rerum natura*, is nothing more than the presence in the body of living growing antigens which excrete toxins definitely selective for certain tissues. To this antigen, the body reacts by producing antibodies. It does not follow that the difference between a non-immunized and an immunized animal lies

in the number of circulating antibodies, for immunity may persist after the disappearance of such antibodies. This type of immunity expresses itself as hypersensitiveness which, with the non-bacterial antigens, may be harmful. But hypersensitiveness to the bacterial antigens may, in some of its aspects, represent an acceleration of the local inflammatory reaction and, in this sense, possess defensive functions.

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drate. The nucleoprotein, Zinsser thinks, has an important bearing on allergy, although it is generally held that nucleoprotein antibodies have no particular protective significance. The carbohydrate, which carries the specificity in the capsule, is capable of combining itself with formed antibody. When dissociated from its protein fraction, it is unable to induce antibody formation. This carbohydrate substance is easily dissociated from its protein mate, is free in exudates or circulation and, by uniting with antibody and diverting it from the organisms, interferes with bacterial destruction, thereby contributing to the virulence of the bacteria. Since it is only the combination of the antigenic fractions which can lead to the type specific antibody formation, the rough organisms—which contain only the protein constituents—though also antigenic, produce antibodies which are not type specific.

This new conception has profoundly altered the methods of preparation of vaccines and sera. In the preparation of vaccines it is essential that the organism used be of the smooth virulent variety, containing the whole antigen and all the antigenic constituents possessed by the mutation form which causes the disease. Heat modifies typhoid antigens. Formalinized antigen is most potent.

An S organism can easily be transformed into the R form not only by cultivation on artificial media, but also most probably in the bodies of patients recovering from pneumonia and diphtheria. The mysteries of rapid rise and decline in mortality in an epidemic may perhaps be explained by this probable transformation by the body of the S into the R form. Morbidity and mortality show a parallel rise as long as S forms present in early cases are spread among susceptibles. Conversely, when the much less virulent R forms come into contact with individuals, mortality decreases accordingly. The present explanation of the appearance of sporadic disease is that R forms are capable of being changed into S forms possessing increased virulence, as shown by Levinthal and Dawson.

Principles governing the resistance of the body to bacterial infection have limited application to tuberculosis and syphilis and still less to protozoal and filterable virus disease. Ultramicroscopic filterable virus immunity differs in its mechanism of production from other types in that active immunity can be produced only after the live virus penetrates the capsule and enters the cell. In rabies

is temporary speeding up of metabolism, an increased concentration of blood enzymes, and an increase of fibrinogen and blood globulin; there is a profound change in the relative distribution of blood in the visceral and splanchnic areas, with consequent effect upon leucocyte distribution and with the development of chills and fever, according to alternating peripheral and visceral vaso-constriction."

Strangely enough, non-specific protein therapy produces specific antibodies. Animals that have once been immunized and allowed to rest until antibodies have disappeared from the circulation may again produce type specific antibodies when injected with non-specific substances such as salt solution.

The problem of the fluctuations of host susceptibility other than that associated with depression, fatigue, *etc.*, has been approached from two different tangents. Draper and Syevek feel that susceptibility, particularly in regard to diseases caused by neurotropic ultra-microscopic viruses, varies with the constitutional type. It is difficult to prove this contention. The other approach is the dietetic relationship to susceptibility. Theobald Smith in 1913 attributed a stable epidemic among guinea pigs to a lack of green food. A vitamin A deficient diet predisposes rats to pyogenic infections. A vitamin B deficient diet increases predisposition of pigeons to the anthrax bacillus and to the pneumococcus. Deficiencies in diet, then, do have an influence like debilitating disease or circulating toxins upon increasing susceptibility, but the manner, direct or indirect, is most uncertain.

Remarkable in the field of immunology is the new conception of the native or sporadic occurrence of disease and of the origin of epidemics. Like other plants, bacteria show many mutations differing morphologically, each with corresponding differences in the virulence and the structure of the antigen. This formation of mutations is known as "bacterial dissociation." Smoothness of the surface of colonies ("S" colonies) growing on agar plates is characteristic of relatively non-virulent organisms. The difference between the virulent and the non-virulent organisms is entirely dependent upon the constituents of the antigen. In the virulent types of non-motile organisms, such as staphylococci and pneumococci, in contrast to more virulent types, there is a complete antigen containing in loose combination two substances—a nucleoprotein and a carbohy-

drate. The nucleoprotein, Zinsser thinks, has an important bearing on allergy, although it is generally held that nucleoprotein antibodies have no particular protective significance. The carbohydrate, which carries the specificity in the capsule, is capable of combining itself with formed antibody. When dissociated from its protein fraction, it is unable to induce antibody formation. This carbohydrate substance is easily dissociated from its protein mate, is free in exudates or circulation and, by uniting with antibody and diverting it from the organisms, interferes with bacterial destruction, thereby contributing to the virulence of the bacteria. Since it is only the combination of the antigenic fractions which can lead to the type specific antibody formation, the rough organisms—which contain only the protein constituents—though also antigenic, produce antibodies which are not type specific.

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prophylaxis and distemper immunization, in which supposedly dead organisms are used, it is strongly suspected that the virus is profoundly attenuated and not dead. It is possible, however, that a massive amount of dead virus may be effective in producing immunization. In an animal immunized with the living virus, it is the body serum and not an antibody which contains the element so antagonistic to the virus that it cannot enter the cell. The defensive element in the serum which tends to persist for years is increased in amounts comparable to antibody production only with the greatest difficulty. It may be that persistence of the virus in tissue after convalescence, as is the case in foot and mouth disease, contagious epithelioma of fowls and in old vaccination areas in rabbits accounts for the prolonged continuous immunity and at the same time indicates wherein the problem of immunization against viruses lies.

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BACTERIOPHAGY

In the Croonian Lecture delivered on December 11, 1930, Bordet¹ reviews the present conceptions of the nature of the bacteriophage. Certain facts connected with bacteriophagy (Twort-d'Herelle phenomena) have been rather definitely established: (1) a surface bacterial culture, grown upon an agar medium, becomes sprinkled with holes; (2) broth to which the active bacteriophage principle has been added becomes unsuitable as a culture medium; (3) a turbid bacterial suspension, made by emulsifying the culture from a solid medium, becomes clear; (4) the active principle regenerates itself in producing its effect; (5) the specificity of this principle is extremely variable and apparently several principles may exist—for example, one principle may attack several related microbial species, but one which acts upon the staphylococcus may not act upon *B. coli*; (6) in some cases the virulence of the principle may be increased by successive transmissions; (7) contact with bacteria sensitive to its action is essential for the reproduction of the principle.

Bordet and Cinca believe, contrary to the view held by d'Herelle,

that the active principle is not a virus but that the bacteria themselves reproduce the lytic principle (bacteriophage). They regard bacteriophagy as a pathologic exaggeration of a physiologic process which, normally, may be related in some manner to the phenomenon of mutation. In support of this view Bordet cited experimental work which demonstrated that two types of the same strain of bacteria (*Bacillus coli*), designated "smooth" and "rough" types, although capable of intermutation by culture, were attacked by preference by different types of lytic principle, termed "weak" and "strong," respectively. Furthermore, as stated by the reviewer, "if the experiment were so planned that the principle acted exclusively on the most sensitive microbes, those regenerated a lytic agent which was so exclusively adapted to them that thereafter it would only act on microbes exactly like them. Thus the individuality of a given type of microbe was reflected in the qualities of the principle which it was capable of elaborating." These observations constitute a distinct advance in our knowledge of microbial physiology, and will undoubtedly lead to a better understanding of effective methods of combating bacterial diseases.

In a study of the relative efficiency and safety of administration of several germicidal agents, Walker made some interesting observations. He found that in the treatment of staphylococcus infections, bacteriophage is more effective than are non-irritating and non-toxic doses of a variety of chemical agents including phenol, bichlorid of mercury, iodine, formaldehyde and chloramine. With the increasing discriminating therapeutic employment of bacterial filtrates it becomes evident that they occupy a distinctly valuable place in the treatment of certain conditions of bacterial origin.

Rice reported the use of bacteriophage preparations in 300 cases of suppurative conditions caused by *B. coli* and *staphylococcus albus* and *aureus*. These included boils, carbuncles, abscesses, cellulitis, cystitis, bed-sores, osteomyelitis, leg ulcers, acne and impetigo. Good results were obtained in 90 per cent. of these cases and no ill effects were observed. The author expresses the belief that stock bacteriophage preparations are satisfactory, but, if desired, potent products may be prepared as follows:

B. coli and *staphylococci* are grown for two to twenty-four hours in meat extract or meat infusion peptone broth. These cultures

are then partially or completely lysed by the addition of active bacteriophage, and, after twenty-four hours, are passed through a Seitz or Berkefeld filter to remove all suspended material.

In the case of superficial lesions the filtrate is applied in the form of a wet dressing. If the process is deep-seated the filtrate may be injected into the lesion or applied as a wet dressing after breaking the continuity of the skin by means of a needle or scalpel. The dosage is of no importance.

REFERENCE

¹ BORDET: *Lancet*, vol. i, p. 79, 1931.

AGRANULOCYTOSIS

THE truth of the maxim, "Any agent capable of doing good is capable of doing harm," has been strikingly emphasized by the numerous recent reports of disastrous effects of arsenic upon bone-marrow function. Farley reported seven cases presenting the clinical picture of agranulocytosis following arsphenamine therapy. The characteristic features of this condition are manifested in the blood picture, consisting of marked anemia, usually of the secondary type, with leukopenia of profound degree (100-2,000) due largely to a decrease in or total absence of granulocytes. Immature cells, including nucleated red cells, are usually not present in the bloodstream; platelets and reticulocytes are diminished in number. Purpuric manifestations with bleeding from mucous membranes and hematuria occur commonly. This condition, first termed agranulocytic angina by Schultz because of its occurrence in association with ulcerative lesions of the mouth and pharynx, is more properly termed agranulocytosis or granulocytopenia. The fundamental fault lies in a depression of bone-marrow function which may apparently result from a variety of causes. Blumer reported its occurrence in association with numerous boils and abscess formation. Otto observed agranulocytosis in a patient with extensive ulceration of the vagina. It has also been found in patients with necrotizing ulcerative lesions of the bladder and rectum.

Arsenic is unquestionably a more frequent offender in this connection than is ordinarily recognized. Lindsay, Rice and Selinger⁴

observed that purpuric manifestations are fairly common following arsphenamine therapy and that such therapy, if continued, may result fatally. Aubertin and Lévy are of the opinion that individual predisposition to arsenic is present in such cases and that alteration in the blood picture is preceded by clinical signs and symptoms of intolerance to the drug. Farley expresses a similar belief. In the presence of such signs as itching, eruptions of a macular, papular or vesicular nature, purpura, fever, malaise or jaundice, the blood should be carefully studied. In the presence of eosinophilia (5-7 per cent.), leukopenia or slight decrease in neutrophiles, the administration of arsenic or mercury in any form should be immediately discontinued and withheld for a variable period of time, in some cases a year elapsing before its resumption.

Stocké divides patients presenting manifestations of this condition into three groups: (1) showing agranulocytosis, (2) in which anemia predominates, and (3) in which hemorrhages and purpuric manifestations are the outstanding features. From a clinical standpoint the gravity of the condition in any individual case appears to be in direct ratio to the degree of granulocytopenia. The mortality is extremely high. With this demonstration of the fact that arsphenamine may be productive of such dire consequences extreme caution should be employed in its administration and the earliest sign of intolerance should be a signal for the immediate cessation of therapy. Farley believes that the benzol radicle may be the offending agent rather than the arsenic constituent of arsphenamine. Prophylaxis, so far as is possible, is of major importance. Active therapy has little to offer. The primary indications are the stimulation of bone-marrow function, the control of hemorrhage and the correction of the anemia. A small proportion of cases recovers spontaneously, and in any case it is probable that the outcome is entirely dependent upon the extent of bone-marrow injury. Numerous methods of therapy have been employed in an attempt to stimulate the bone-marrow, among them liver therapy and the production of fixation abscesses and therapeutic fever. In those cases which follow the administration of arsphenamine, sodium thiosulphate has been used with questionable effect. Friedemann and Elkeles⁷ report eminently successful results by the use of Roentgen-ray therapy in stimulating doses. Recovery occurred in thirteen of fifteen un-

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complicated cases, improvement in the blood picture being noted within twenty-four hours. In all cases small, frequently repeated blood transfusions should be routinely administered, accomplishing the dual purpose of stimulation of hematopoiesis and correction of the anemia. Blood transfusion and stimulating irradiation constitute perhaps the most satisfactory means of combating a condition the mortality of which in 136 cases collected by Hodges⁸ is 85.8 per cent.

It is interesting to note that Brown described this (*American Medicine*, 3:649, April 19, 1902) condition under the title, "A Fatal Case of Acute Primary Infectious Pharyngitis, with Extreme Leukopenia," more than twenty years before the work of Schultz was published.

PERNICIOUS ANEMIA

Perhaps the most important contribution to medicine within the past five years is the increase in our understanding of certain factors concerned in the etiology of pernicious anemia. The therapeutic effects of liver, kidney, and potent extracts of those organs in producing remissions in pernicious anemia with symptomatic relief and restoration of the normal blood picture have been well established. A natural consequence of the brilliant pioneer work of Minot and Murphy and their collaborators was the belief that pernicious anemia is the result of deficiency in some substance elaborated by the liver or some other organ which had been demonstrated to exert a beneficial effect upon the course of the disease. The stomach is the only organ in which either functional or anatomical change has been consistently demonstrated in this condition. The association of achylia gastrica and pernicious anemia has been recognized for many years but the recent work of Castle and his associates has thrown a flood of light upon the etiological significance of this relationship.

Castle and Townsend demonstrated that the interaction of normal gastric secretion with beef muscle results in the production of a substance which is effective in a manner similar to liver in promoting blood regeneration in pernicious anemia. It was further shown that the interaction of beef muscle with gastric juice secreted by individuals with pernicious anemia is ineffective in this respect. In recent communications Castle, Townsend and Heath extend their observations and further clarify the result of their experiments in the following conclusions:

(a) Two factors are essential for normal erythropoiesis: (1) the "intrinsic factor" is apparently secreted by the gastric mucosa and is not demonstrable in the secretions of other portions of the gastrointestinal tract; (2) the "extrinsic factor" present in beef muscle, probably protein in nature, and capable of interacting with the "intrinsic factor" with the consequent production of an agent or substance which produces a characteristic hematopoietic response in pernicious anemia patients.

(b) The "intrinsic factor" is not present in the gastric secretion of individuals with pernicious anemia. The lack of this factor is, in all probability, the essential defect leading to the development of the disease.

(c) In rare instances of pernicious anemia hydrochloric acid may be present in the stomach; in such cases the "intrinsic factor" is absent. Conversely the gastric juice of individuals with achlorhydria without pernicious anemia contains this factor. Since there may exist dissociation of the essential substances secreted by the gastric mucosa it follows that the ordinary tests for the determination of hydrochloric acid and peptic activity are not conclusive in determining the presence or absence of the "intrinsic factor."

These observations have been furthered and substantiated by the successful results obtained by feeding hog stomach or extracts of that organ to patients with pernicious anemia. It is now apparent that a hitherto unrecogized clinical concept has arisen. Pernicious anemia must be considered in the nature of a deficiency disease; not, however, in the ordinary sense of vitamin or endocrine deficiency, but as characterized by the lack of an essential substance (intrinsic factor) which, through its interaction with another substance (extrinsic factor) normally produces an agent necessary for normal hematopoiesis.

SECONDARY ANEMIA

Following the demonstration of the efficacy of liver extract in the treatment of pernicious anemia it was natural that it should be employed extensively in the presence of secondary anemia. The reported results have been, in the main, disappointing. Whipple, Robscheit-Robbins and Walden have pointed out, however, that whole liver possesses a capacity for stimulation of hemoglobin for-

mation in the hemorrhagia anemias which is not possessed by the extracts effective in pernicious anemia. They have furthermore succeeded in extracting a liver fraction, constituting 3 per cent., by weight, of whole liver, which contains 65-75 per cent. of the potency of the latter in stimulating hemoglobin formation in hemorrhagic anemias. The effect of this substance may be enhanced by the supplementary administration of iron. It appears that whole liver possesses hematopoietic properties apart from its pernicious anemia fraction, and that liver therapy in secondary anemias should not be abandoned without a fair trial.

IRON THERAPY IN ANEMIA

The pertinent observations of Ricker have conclusively demonstrated that the administration of iron in pernicious anemia is illogical. In this condition, as well as in all hemolytic anemias, iron is present in the blood serum in larger amounts than in normal serum, returning to normal during remissions. In hemorrhagic anemias and in the presence of deficient quantities of iron in the diet, the content of iron in the serum becomes subnormal. In view of such facts the routine employment of iron in all types of anemia is to be discouraged. It can obviously do no good, and may conceivably be productive of harm if forced upon an organism which is unable to utilize the excessive amounts already present in the circulation.

ANEMIA IN SPRUE

The similarity between the anemia commonly associated with sprue and that characteristic of pernicious anemia has led to the therapeutic use of liver, liver extract and stomach extracts in the former condition. The diagnostic and therapeutic problems associated with sprue are of general interest because of the increasing realization that its occurrence must not be considered as confined strictly to tropical climates. Castellani found that liver, pancreatic and stomach extracts were useful in the treatment of sprue, the last-named being most effective. Porter and Rucker administered 630 gm. of raw liver daily with prompt improvement in two cases of non-tropical sprue. There was striking relief from the existing intestinal disturbance as well as from the manifestations of anemia,

which, in these cases was associated with megaloblastic hyperplasia of the bone-marrow. The authors believe that these observations suggest that sprue is a deficiency disease, closely related to pernicious anemia, and rather militate against the theory of the etiological relation of *Monilia* to this disease.

Ashford, however, adheres to the view that the etiology of sprue is still unknown and that the anemia which may be associated with it is extremely variable in character. He states that the anemia of sprue may be of three varieties, (1) dysplastic, (2) hypoplastic, or (3) aplastic. The first, dysplastic or megaloblastic, is the only form which responds favorably to liver therapy. In certain cases refractive to other modes of treatment, improvement has followed the administration of *Monilia psilosis* vaccines.

TRYPARSEMIDE AMBLYOPIA

Casten reports the occurrence of permanent subjective and objective visual disturbances in 2 per cent. of 1254 patients receiving tryparsamide. Temporary disturbances are much more common. These untoward manifestations are believed to be due to a toxic effect of tryparsamide upon the optic nerve which it reaches by way of the subarachnoid and subvaginal spaces. In the treatment of the acute stages of this condition good results were obtained by the system of forced drainage of cerebrospinal fluid described by Kubie in 1923, the technic of which is as follows:

Lumbar puncture is performed and the needle left *in situ* for two hours, during which time 2 liters of water are taken by the patient. At the end of one hour, 50 cubic centimeters of doubly distilled water are injected intravenously slowly and an ampoule of obstetrical pituitrin is administered at the same time. One hundred and fifty cubic centimeters of spinal fluid are withdrawn. This procedure is repeated in twenty-four hours and again in a few days if necessary. Casten reports remarkable improvement in vision and hearing following this procedure.

DISSEMINATED SCLEROSIS

With the exception of lues, disseminated, insular or multiple sclerosis is perhaps the most common organic disease of the central nervous system. Because of its generalized nature, it usually leads

to complete disability and is particularly unfortunate in that it commonly affects young adults in previously good health. The announcement of the discovery of the etiological agent responsible for the production of this disease must receive careful consideration. Chevassut reports the isolation of a filterable virus, designated *Spherula insularis*, recovered by culture from the cerebrospinal fluid of 176 out of 189 cases of disseminated sclerosis. The virus was inoculated into a series of monkeys, one of whom subsequently developed paralytic symptoms. The observations of Chevassut have been confirmed by Ransome and Smith. Belief in the infective etiology of this disorder is not new. Gye in 1913, Kuhn and Steiner in 1917, and Adams, Blacklock, Dunlop and Scott in 1924, reported the development of paralytic symptoms in animals which had been inoculated with cerebrospinal fluid withdrawn from patients with disseminated sclerosis.

The etiological relation of *Spherula insularis* to this condition has been in a sense substantiated by the work of Sir James Purves-Stewart who reported encouraging results obtained by the therapeutic use of a vaccine prepared from the virus. Improvement was noted in nine of ten early cases and in twenty-two of twenty-seven moderately advanced cases. Hicks, Hocking and Purves-Stewart believe that the most satisfactory results are obtained by the intravenous injection of the vaccine. There is also some evidence that inhibitory substances are formed in the blood serum of patients and rabbits in whom the virus suspension had been injected. No such substances were demonstrable in the blood serum of monkeys similarly treated. The fact that the virus has been found to be still present in the cerebrospinal fluid in sixty-two of seventy cases of disseminated sclerosis after vaccine therapy does not preclude the possibility of symptomatic cure in those cases as is exemplified in other chronic infectious diseases, notably tuberculosis and lues.

HERPES ZOSTER

The pain associated with herpes zoster is at times excruciating and frequently responds to none of the remedial measures ordinarily prescribed. Sidlick reports the use of obstetrical pituitrin in a large series of cases. Prompt relief from pain was usually secured following one or two intramuscular injections of 0.5-1 cubic centi-

meter each at intervals of twenty-four hours. The mode of action of pituitrin in herpes zoster is conjecturable, but the reported consistently beneficial effects of this mode of therapy warrants its trial in all cases. The only practical contra-indications are pregnancy and hypertension.

PNEUMONIA

Despite active bacteriologic and serologic investigations the mortality of pneumonia in large series of collected cases has remained unchanged. It is true that in isolated instances, in specially equipped clinics, serum therapy appears to have been of some benefit, but, in sharp contrast to results obtained in the treatment of other acute specific infectious diseases, those reported generally in pneumonia are practically the same as they were in the days when Osler practiced medicine in Philadelphia and Baltimore, and wrote in a similar vein of his period and of that which preceded him. The recent investigations of Henderson, Haggard, Coryllos and several others, along entirely different lines from those previously followed, constitute a distinct advance in our understanding of the pathologic physiology of this disease and indicate a rational and apparently effective mode of therapy.

The work of Coryllos, summarized in a recent contribution and amply confirmed by several authors, strongly suggests that pulmonary atelectasis, due to preoperative or postoperative bronchitis, is not only the forerunner of postoperative pulmonary complications (pneumonia and bronchopneumonia), but that it plays an essential part in the development of those conditions. This concept may be best presented in the words of the author. "Bronchial obstruction is the starting point of pneumonitis, lobar or lobular, and most probably also of abscess and gangrene as well. The particular condition arising will depend upon the infecting agents. So long as the bronchi are open and their drainage insured, the lung maintains asepsis by the mechanical means at its disposal—evaporation, expectoration, activity of the ciliary epithelium, and the anti-septic power of the mucus (Arloing); but when obstruction occurs, the fate of the parenchyma depends upon the microbes present in the occluding mucus. If they are of low virulence, there will be a slight degree of inflammation, a slight amount of exudate, and little

or no fibrin. The air will be absorbed, and the walls of the alveoli will collapse completely, reducing to a minimum the size of the lung with marked displacement of the mediastinum, heart and trachea, and with elevation of the diaphragm. If the mucus be infected with more virulent pneumococci, then a condition called postoperative pneumonia (postoperative pneumococcal atelectasis), lobar or lobular, will develop. The amount of exudate will be greater and consequently the decrease in the size of the lung less marked and the displacement of the mediastinum less conspicuous. If pyogenic micro-organisms are present (*staphylococcus*, *streptococcus*, influenza bacilli, *etc.*) abscess may result if the occlusion is sufficiently prolonged. If, finally, virulent anaerobes are present, gangrene may ensue."

Similar principles have been postulated as existing in "medical" pneumonia as well as in postoperative pneumonia, both conditions representing essentially an infected organ with lack of drainage. This view of the etiological significance of atelectasis in pneumonia is supported by the demonstration of the fact that, contrary to the prevailing view, the heart and trachea are always displaced toward the pneumonic lung in medical pneumonia as well as in pulmonary atelectasis and postoperative pneumonia. In accordance with fundamental surgical principles it is vitally important, since infection takes place by way of the respiratory passages, that these passages be kept open in order to secure good drainage. One of the most important natural mechanisms with which the respiratory tract is endowed which favors the outward movement of foreign matter is embodied in the respiratory movements, which are probably accompanied by alternate contractions and relaxations of the bronchial tree. The importance of this mechanism for protection of the lungs against infection is evidenced by the demonstration of the fact that the mere introduction of pathogenic organisms into the lungs is not capable of producing pneumonia in dogs; the animals must, in addition, be so treated that the respiratory movements are depressed and the cough reflex abolished. The natural conclusion which was reached as a result of extensive physiological and clinical investigation was that, considered generally, slow, shallow breathing favors the development of pneumonia while deep breathing with adequate pulmonary ventilation tends to prevent it.

In accordance with these fundamental principles, Henderson, Haggard, Coryllos, and Birnbaum have advocated the use of carbon dioxide and oxygen inhalation in the treatment of pneumonia. Henderson and Haggard had previously shown that the inhalation of carbon dioxide is capable of preventing the development of pneumonia in several clinical conditions including carbon monoxide asphyxia. The beneficial effect is assumed to be due to the fact that this procedure results in stimulation of the respiratory center, increased respiratory movements, hyperventilation, and the prevention or correction of atelectasis. Henderson, Haggard, Coryllos and Birnbaum succeeded in producing pneumonia of marked virulence in sixteen dogs by anesthetization with iso-amyl-ethyl barbituric acid and the insufflation, through the bronchoscope, of concentrated suspensions of virulent cultures of pneumococcus type II. After spending from two to twenty-four hours in an atmosphere of 5-7 per cent. carbon dioxide in oxygen all but three of the animals made a perfect recovery. The experience of the authors indicates that, under ordinary conditions, few if any would have survived. Roentgen-ray examinations revealed that atelectasis was a prominent feature in all of the cases of pneumonia and that under the influence of carbon dioxide inhalations, reinflation of the affected lobes occurred in every case. These observations afford strong support to the belief of Coryllos and Birnbaum that lobar pneumonia is a pneumococcic atelectasis. It appears, furthermore, that carbon dioxide decreases the hydrogen-ion concentration of the exudate, favoring fibrinolysis and liquefaction and also directly inhibits the growth and virulence of the pneumococcus. Henderson and his collaborators include a preliminary report of the results of carbon dioxide-oxygen therapy in a series of 126 patients with pneumonia. Of this number only nine died, nearly all of whom were treated only in the later stages of the disease. In a large group receiving routine treatment the mortality was 31 per cent.

The recommended technic is as follows:

A 5-10 per cent, mixture of carbon dioxide in oxygen is administered by means of an inhalation mask or through a nasal catheter for periods of five to ten minutes every two to three hours, under a pressure of approximately 10 pounds. Immediately after the first few inhalations the respiratory movements are observed to become

deeper. The quantity of the mixture may be regulated so that its administration may be continued for the required time without undue respiratory difficulty. The use of the respiration chamber or tent is, of course, the method of choice, but the nasal catheter or mask, if tolerated, may serve as effective substitutes. The use of oxygen alone frequently fails to accomplish the desired effect because of the existence of a state of central respiratory depression with consequent shallow breathing which, far from being corrected, may be aggravated by oxygen inhalation. The addition of carbon dioxide stimulates the depressed respiratory center, producing adequate ventilation and, through effective absorption and circulation of the oxygen, correction of the existing state of anoxemia.

Any therapeutic procedure which is based upon so firm a physiologic foundation and so carefully studied experimental and clinical evidence must be accorded careful consideration. Because of its freedom from danger the use of carbon dioxide-oxygen inhalation in pneumonia should be given a thorough trial. Its practically specific effect in the prevention and treatment of postoperative pulmonary atelectasis and carbon monoxide asphyxia give promise of its increasing scope of usefulness in the treatment of pneumonia.

ELECTROLYTE STUDIES IN PNEUMONIA

Remarkable progress has been made in the past few years in the study of disturbances of electrolyte balance in several pathological states and in the realization of the metabolic derangements incident to such changes. The decreased urinary excretion of chlorid in pneumonia has been recognized for many years and was attributed to its retention in the diseased lung, from which it was liberated during and after the period of crisis. Careful studies of serum electrolytes in pneumonia later revealed that among other changes there occurred a diminution in the concentration of chlorid in the serum. This is associated with a normal serum bicarbonate content. These observations have recently been confirmed by Atchley and Benedict.

The clinical significance of plasma chlorid concentrations has been well demonstrated in studies of acute intestinal obstruction. It is now well recognized that hypochloremia plays an important part in the causation of the toxemia so prominently manifested in

that condition. The prompt symptomatic relief which follows the administration of sodium chlorid to such patients is little short of miraculous. The elucidation of the essential rôle of plasma chlorid in the maintenance of the normal acid-base equilibrium and the normal respiratory exchange has resulted in further advances in our understanding of its clinical significance in disease states. Alkalosis and anoxemia are natural consequences of hypochloremia, both being potential and actual sources of great harm to cellular functions throughout the body. In pneumonia, a condition in which the nature of the lesion tends in itself, by causing hyperventilation and diminished aërating surface, to produce anoxemia and alkalosis, the superimposition of the added factor of the hypochloremia is particularly dangerous.

The administration of sodium chlorid orally, by proctoclysis and parenterally has been suggested for the relief of the toxic manifestations of lobar pneumonia. Scholtz⁶⁴ is one of the recent advocates of this procedure. He suggests that 10 gm. of sodium chlorid be given daily in addition to the regular diet. In certain cases it may be administered by rectum, subcutaneously or by the intravenous route. If given intravenously, 100 cubic centimeters of a 10 per cent. solution may be injected very slowly; the presence of marked circulatory weakness contra-indicates this mode of administration.

It appears likely that sodium chlorid therapy and carbon dioxide-oxygen inhalation, based as they are upon sound physiological principles, constitute important additions to the therapy of lobar pneumonia.

UNDULANT FEVER

In 1887, Bruce¹ reported the isolation of an organism, designated *Micrococcus melitensis*, from the spleen of a patient who died of undulant fever. In 1897, Bang² isolated a small bacillus, *B. abortus*, which often appeared coccoid in shape, from cattle suffering with contagious abortion. It was not until 1918, however, that the relationship between the two conditions was recognized and described by Evans.³ Since that time the disease, as it occurs in man, has been thoroughly studied from the standpoints of etiology, epidemiology, and laboratory diagnosis. Agglutination tests form the most definite means of diagnosing infection with the *Brucella melitensis* organisms. Epidemiologic data indicate that cattle and hogs

with contagious abortion are the chief source of this infection in man. A recent report by Broadbent⁴ indicates that other sources must be considered. His patient, a child aged three and a half years, was infected by contact with goats which were subsequently found to be infected with *B. abortus*. It is evident that infection may occur not only from milk, cream and cheese, but also from materials contaminated with the urine of infected animals, the organisms being excreted by the kidneys for considerable periods of time.

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- ² BANG: *J. Comp. Path. and Therap.*, vol. 10, p. 125, 1897.
- ³ EVANS: *J. Infect. Dis.*, vol. 22, p. 580, 1918.
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ATYPICAL TYPHOID INFECTIONS

The relatively low incidence of typhoid infection in urban communities has undoubtedly resulted in a failure of recognition of many atypical manifestations of that condition. Gray³³ has pointed out some of these atypical manifestations presented by patients suffering with *B. paratyphosus B.* infection.

The symptoms are referred chiefly to the gastro-intestinal tract, generalized abdominal pain, vomiting and diarrhea being commonly present. The abdominal wall is soft with but moderate tenderness, and only slight rigidity. The rise in temperature is not of the characteristic step-like nature usually seen in enteric fever and the fever is of variable duration, ranging from four to eighteen days in the cases observed. The condition may be mistaken for appendicitis or gall-bladder disease. One of the outstanding features of such infections is the fact that the degree of toxemia is out of all proportion to the subjective and objective manifestations.

All such cases must receive thorough bacteriological study. Cultures of the urine, faeces and blood may reveal the offending organism. Serum agglutination tests for *B. typhosus* and *B. paratyphosus A* and *B* should be performed. In some cases, as in one reported by Gray, the organism may be found only in the wall of the gall-bladder. The realization that a variety of gastro-intestinal disturbances accompanied by fever and toxemia may be due to typhoid

or, more commonly, to paratyphoid infection, is the first essential step in arriving at the correct diagnosis of the condition. It is probable that with these facts in mind, the extremely common but highly unsatisfactory diagnosis of "intestinal influenza" will be made less frequently.

ACUTE ANTERIOR POLIOMYELITIS

The use of convalescent serum in the treatment of acute anterior poliomyelitis has passed beyond the experimental stage. Its value appears to be fairly well established. In view of this fact, the recent demonstration of the presence of anti-viral bodies in the blood-serum of apparently healthy individuals is of the utmost practical importance.

Aycock and Kramer report that the serum of 75 normal individuals possessed the property of neutralizing the poliomyelitis virus. Shaughnessy, Harmon and Gordon, found that the serum of children under 2 years of age had no such effect whereas that of children above 2 years of age exerts the same influence upon the virus as does convalescent serum. A probable explanation for these observations has been advanced by Fairbrother and Brown. They believe that the presence of anti-viral bodies in the blood of normal individuals is due to the previous existence of subclinical poliomyelitis infections. Thus the serum of contacts who had never manifested symptoms of the disease may contain poliomyelitis antibodies.

It appears probable, therefore, that the incidence of acute anterior poliomyelitis infection is far greater than has been supposed and that, fortunately, in the great majority of instances, the manifestations of involvement of the central nervous system are absent. The therapeutic significance of these observations is apparent; the serum of normal individuals who have never been known to have had the disease may be employed with fairly definite assurance of its anti-viral potency.

CINCHOPHEN INTOXICATION

It is extremely distressing and certainly disconcerting to learn that a therapeutic agent which is as widely employed as cinchophen has been for the past fifteen years is productive of such ill effects as

have recently been forced upon the attention of the medical profession. The harmful results which may attend the use of cinchophen or any closely related substances are dependent upon their selective affinity for the liver. As stated by Rabinowitz, the hepatic lesions which have been observed consist of atrophy, regeneration, cirrhosis and nodular hyperplasia. These pathological changes are typical of the response of the liver to the action of any hepatic poison, such as chloroform, carbon tetrachloride and phosphorus. The acuteness and degree of severity of both the pathological lesions and the symptomatic manifestations are dependent upon several factors. Among these are the previous condition of the liver, its susceptibility to injury, the amount of the noxious agent administered and the period of time over which its action has continued.

An important source of danger lies in the apparent wide variation in individual susceptibility of the liver to injury by toxic agents. This is emphasized in the case of a patient observed by Stacy and Vanzant, who had taken one to three tablets of cinchophen daily over a period of six weeks. One week later jaundice was noted and death rapidly ensued with manifestations of acute yellow atrophy or acute toxic necrosis of the liver. Vajda recently reported the occurrence of acute hepatitis in two patients due to cinchophen intoxication. Other individuals are exposed to similar doses for much longer periods with no clinical evidences of hepatic damage.

Several factors may be responsible for this variable response. There may, of course, exist an inherent difference in susceptibility of the liver to injury, or the functional reserve capacity of that organ may be diminished owing to the presence of undemonstrable hepatic disease. It is now well recognized that, fortunately for the individual but unfortunately from the standpoint of early diagnosis, moderately advanced grades of hepatic disease of a chronic nature may exist in the total absence of any manifestations of functional insufficiency demonstrable by present methods of investigation of liver function. This is due to the enormous power of regeneration possessed by hepatic tissue, and to the large functional reserve capacity of the liver.

Recent years have witnessed the growing realization of the fact that the resistance of the liver to injury by either bacterial or chemical agencies is dependent to a considerable extent upon the amount

of glycogen stored in that organ. Any disease process or dietary insufficiency which decreases the quantity of hepatic glycogen predisposes the liver to damage by toxic substances. Conversely, any measure which can effectively maintain the reserve glycogen at a high level serves to protect the liver against such injury. Rabino-witz, therefore, recommends the administration of a diet high in carbohydrate, and perhaps insulin, in cases in which cinchophen must be taken over long periods of time. In the event of the development of manifestations of hepatic damage dextrose should be supplied by intravenous injection. Weigeldt recommends the use of lactic acid, sodium chlorid solution, and dextrose and insulin intravenously in such cases. He does not believe that the administration of alkalis is a safeguard against the development of hepatic lesions.

In 1928 Minot and Cutler reported the observation of an increase in guanidine or some closely related substance or substances in the blood of dogs during intoxication produced by chloroform and carbon tetrachloride. This was followed by a diminution in the blood-sugar concentration which fell to extremely low levels in many instances. The chief constant pathological lesion associated with the intoxication resulting from the administration of these substances was an acute and severe central necrosis of the liver. The same authors made the interesting and significant observation that calcium salts exert a highly protective influence both in preventing and treating these intoxications. The probability was naturally considered, as they say, that "when similar liver injury has been caused in some way other than by the administration of these drugs, similar abnormalities and symptoms may be looked for, and if present might also be relieved by calcium therapy." The truth of this hypothesis received substantial support by studies of patients with acute hepatic injury following arsphenamine therapy, pre-eclamptic toxemia and eclampsia. The administration of calcium salts resulted in marked symptomatic and objective improvement. Patients with chronic hepatic disease presented none of the above mentioned characteristic blood chemical features.

The observations of Minot and Cutler have been amply confirmed by other investigators. Ellsworth found an increase in blood guanidine in six patients with arsphenamine hepatitis. Findlay and

Hindle reported an increase in the quantity of guanidine-like substances in the blood of monkeys in experimentally produced yellow fever with acute hepatic necrosis. The administration of calcium lactate, although it did not prevent death, did exert a beneficial influence upon certain symptomatic manifestations, particularly hemorrhage. Recently Cutler reported the successful use of calcium therapy in combating the toxic effects of chloroform, carbon tetrachloride, arsphenamine and phosphorus in dogs. Similar results were obtained in patients with acute hepatic disease.

In view of these studies it would appear that the rational therapy of clinical conditions associated with acute liver damage should include the following measures:

- (1) A high carbohydrate diet to ensure the maintenance of an adequate reserve supply of glycogen in the liver. The routine administration of insulin is not indicated, and in many cases is distinctly contra-indicated. Intravenous dextrose may be required.
- (2) A low protein intake to keep the production of guanidine (imido-urea) at as low a level as possible.
- (3) The administration of calcium salts.

Perhaps the most satisfactory preparation of calcium for routine use, either orally, intramuscularly, or intravenously, is calcium gluconate. It may be administered orally in the dosage (adults) of 60 grains three or four times daily, one-half to one hour before meals, and intramuscularly or intravenously in the dosage of 10 c.c. of a 10 per cent. solution.

It would also appear logical to assume that in cases which demand the use of cinchophen in large doses over long periods of time the above régime should be instituted in order to prevent, so far as is possible, the development of acute and frequently fatal hepatic insufficiency.

JAMAICA GINGER PARALYSIS

Many reports have appeared during the past year of a peculiar atypical form of paralysis apparently dependent upon a peripheral multiple neuritis, the condition being definitely associated with the ingestion of fluid extract of ginger. The term "Jamaica Ginger" paralysis is evidently a misnomer inasmuch as that substance is clearly not responsible for the production of the condition noted

in these cases. The active ingredient has been carefully investigated by the United States Public Health Department. The preliminary report of these studies has been published by Smith and Elvove. The decision reached by the investigating committee was that a shipment of ginger root had probably been contaminated with another root which bears a superficial resemblance to ginger and which is capable of affecting the peripheral motor nerves; such plants are known to exist. Another possibility which suggests itself is that some poisonous agent somehow became incorporated in the ginger extract during the process of its manufacture and was so altered through the action of the ginger or alcohol, or both, as to prevent its chemical identification. The toxic substance is believed to be a stable combination of phenols (tri-ortho-cresyl-phosphate).

The large number of cases reported by several authors and occurring within a relatively brief space of time is indicative of the widespread use of Jamaica ginger extract as an alcoholic beverage. Bennett, reported a series of ten cases, Burns, fifty cases treated within two months, Merritt, Houston and Moore, fifteen cases. Other large series have been reported by Goldfain, and by Harris. The report published by Smith, includes over 200 cases observed in Ohio by Le Blanc within a few months and 119 occurring in Tennessee. Many other isolated cases have been recorded.

Manifestations of the condition usually occur within one to three weeks after drinking the ginger extract. The earliest symptoms are usually sensory in nature consisting of aching sensations in the leg muscles, particularly the calves, and coldness and tingling of the toes and feet. Pain is not a prominent feature. These sensory phenomena are of relatively brief duration, being superseded, after one or two days, by evidences of motor involvement. The anterior tibial groups of muscles are usually the first to be affected, one side being at times involved earlier than the other. Eventually, and usually rapidly, bilateral foot-drop develops with ataxia. This is frequently followed by weakness and paralysis of the muscles of the hand and forearm, resulting in bilateral wrist-drop. The upper arm has not been involved in the paralytic process and the muscles of the thigh are affected only in advanced cases. The deep reflexes are extremely variable, differing in this respect from other types

of peripheral neuritis. The tendo achillis jerk is practically always absent, indicating the rather constant involvement of the peripheral portions of the affected nerves. The patellar, biceps, and triceps reflexes may be normal, exaggerated, diminished or absent. In some cases, but rarely, a plantar extensor response (Babinski) has been observed, with a typical defense reaction suggesting pyramidal tract involvement. In a few instances the cerebrospinal fluid protein has been found to be slightly increased and abnormal colloidal gold reactions have been reported. Trophic changes have been noted, such as brawny desquamation of the skin of the palms, glossy, tight skin, and, occasionally, slight edema. Vasomotor phenomena are rather common, including profuse perspiration of the affected parts, mottling, cyanosis and hypothermia. There may be minor alterations in vibratory and muscle sense, but pain, temperature and tactile sensation is usually unimpaired. If the condition progresses, the affected muscles become atrophied, the interossei being particularly affected in this respect. No mental or cranial nerve symptoms have been observed in uncomplicated cases.

In the absence of any definite knowledge of the specific etiology of this condition the plan of treatment must conform to that advocated for other forms of multiple peripheral neuritis. The high incidence of this peculiar affection and its sudden appearance in epidemic form should warrant a careful watch for its early manifestations, and a thorough search for the toxic agent responsible for its development.

PAROXYSMAL HYPERTENSION

Labbé, Violle and Azérad had under observation a patient, aged twenty-nine, who for nine years prior to his death had suffered with recurrent attacks of paroxysmal hypertension. Autopsy revealed, in addition to atheromatous changes in the aorta, and chronic nephritis, an adenoma of the adrenal medulla. The interesting point is raised as to the possible relationship between the paroxysmal hypertensive attacks and the adrenal tumor. Similar cases have been recorded, and, although fluctuations in blood-pressure are recognized as of common occurrence in chronic nephritis and arteriosclerosis, the possibility of such a relationship is not to be ignored.

ANGINA PECTORIS

Levine, Ernstene and Jacobson made the interesting observation that the subcutaneous administration of 1 cubic centimeter of epinephrine to patients with angina pectoris results in the production of an attack. In such patients the rise in blood-pressure and increase in heart rate following the injection of epinephrine are greater than ordinarily occur in normal individuals. This procedure is suggested as a possible test to aid in the establishment of the diagnosis in doubtful cases.

The practical usefulness of such a test must of necessity be extremely limited since, apart from the suffering produced, the dangers incident to an attack of angina pectoris are well known. Because of the wide variation in severity of individual seizures extreme caution must be employed even in supposedly mild cases, particularly since the response to epinephrine occurs in individuals with normal or subnormal blood-pressure as well as in the presence of hypertension. Perhaps the most important practical point which becomes apparent as a result of this study is the danger of administering epinephrine and perhaps ephedrine to patients with angina pectoris. In such cases the use of these agents, even though indicated, must be undertaken with full realization of the attending dangers and only after careful consideration of the possible serious consequences.

ANGINA PECTORIS AND ITS TREATMENT

There is an unfortunate tendency, according to McCrae,¹ to consider the symptoms of angina pectoris as due exclusively to coronary artery or heart disease. What about those cases, he remarks, in which there are severe attacks of angina pectoris over many years? If each attack is associated with pathological changes such as occlusion of minute vessels in the coronary distribution, there hardly seems enough vascular territory to supply sufficient material. Even acute coronary artery occlusion has been considered by some a special form of angina pectoris. The misfortune lies in the tendency to put under one heading a condition with definite clinical features and a positive lesion, and a group which is very much less definite. In acute coronary artery occlusion there is very definite etiology and pathology with a prognosis that can be estimated easily. On the

other hand, angina pectoris is a syndrome with uncertainty as to the cause in some cases, without a definite pathology and with an uncertain outlook.

The features usually regarded as characteristic of angina pectoris are: severe pain referred to some part of the sternum or beneath it, or, according to Brown,² who takes exception to the prevailing opinion, referred to the apical region; an immediate causal feature such as exertion, emotion, anger, a heavy meal or exposure to cold; immediate enforced cessation of activity; radiation of pain; sweating; relief through rest, nitrites and morphia, quick recovery (within a few days at most).

The etiology, McCrae remarks, is probably multiple. In some cases it may be attributed to disease of the aorta, in other cases to disease of the coronary arteries and myocardium. The puzzling group of cases characterized by esophageal or gastric symptoms may etiologically be placed in the viscero-sensory reflex category. One notable case is reported in which a gastric lavage at the first sign of distress brought relief. The total lack of uniformity of pathological changes is confirmed by Romberg,³ who collects a group of cases of angina pectoris in which careful necropsy studies failed to reveal any coronary artery disease. Levy,⁴ too, reports such a case. The phenomena of angina pectoris, according to Wright,⁵ may be due to an exaggerated visceral reflex of which the depressor nerve forms the chief afferent path. Disease of the aortic arch (Allbutt) or over-stretching of the heart by a sudden increase in blood-pressure stimulates the depressor nerve so much so that the normal protective reflex may be carried to an extreme or harmful degree.

In most of the cases coming to necropsy (Thayer⁶), there are, as a rule, evidences of changes in the coronary circulation. The uncommon aortic lesions held responsible are those involving the orifices of the coronary arteries. In few instances of angina which are carefully studied anatomically is there failure to find at necropsy rather definite coronary changes. In the spasmodic attacks which begin and run their courses like spasms of involuntary muscle, being relieved by such antispasmodics as the nitrites, the necropsy findings are usually those of disease of the coronary vessels associated with numerous sclerotic patches. These patches have probably been pro-

duced by gradual occlusion of terminal arteries. Thayer makes the further observation that the most exquisite and persistent and unrelievable pain may follow occlusion of a coronary artery. There is little doubt in the mind of Hamman⁷ that angina is frequently the result of coronary occlusion. It is an angina similar to that of angina pectoris, but it is more severe and prolonged. It persists for hours or days and is relatively unaffected by morphia.

The problem of the cause of angina pectoris, so difficult to untangle, is seen by Brown² from a somewhat different viewpoint. He feels that the explanation of all cases of angina is impossible without invoking the aid of coronary spasm—the spasm occurring in the first part of the aorta or in the coronaries, or in both. It is still an open question, however, as to whether a sudden myocardial ischemia (presumably responsible for the pain) is produced by coronary artery spasm or whether it is due to the inability of stenosed diseased coronaries to meet the extra demands imposed upon them by increased cardiac activity.

Wasserman⁸ believes that the angina is largely a matter of coronary spasm. He hesitates to press this view to include cases in which there is sclerosis and calcification of the coronaries.

Treatment.—It was noted by Vaquez and his colleagues⁹ that the giving of insulin to diabetics with angina pectoris often relieved the anginal attack. Further investigation into this very important observation disclosed that a pancreatic substance mixed with the insulin, and not insulin itself, had relieved the attack. Accordingly the substance was isolated and studied by Gley and Kisthinos:¹⁰ it was found to be a pancreatic extract which contains neither peptone, histamin nor chlorin and was given the name "angioxyl." When injected intravenously into dogs it produced a moderate drop in blood-pressure. Angioxyl is entirely non-toxic and has no effect upon hyperglycemia.

In the twenty cases which have been treated with this "new" drug, fourteen have received complete relief. In the remaining six cases there was an amelioration of symptoms. The treatment comprises a rather extensive series of injections. Ten daily intramuscular injections of 9 to 20 units each initiate the treatment. After a brief interval, another series of ten injections, this time of 40 units each, is given. Still later, a third series of from 40 to 60 units a

dose may be given. The treatment begins to show its effect after about the sixth dose. The unit-mentioned has been standardized so that one "hypotensive unit" is that amount which when injected intravenously into a 2-kilogram dog just barely causes a drop in blood-pressure. As to the mode of action of angioxyl, Vaquez expresses the view that its value is to be ascribed not to its depressive effect upon the blood-pressure but rather to its "trophic action" on the cardiac muscle.

The muscle extract treatment of angina pectoris is still too new to allow commentation. Its adherents differ in their views as to its mode of action but agree that it is a remedy of promise. Schwarzmann¹¹ reports seven cases from a large series in which he employed the extract. The patients selected were those with very severe anginal attacks occurring at frequent intervals. Using muscle extract in doses of 1 to 2 cubic centimeters he obtained prompt relief from painful seizures after one or two doses even in those with coronary and aortic sclerosis. This relief lasted one to four days. When the doses were repeated at intervals of two to three days for several doses the symptoms were relieved for weeks. Schwarzmann expresses the idea that angina pectoris may be due either to the absence of a hormone necessary to the heart or may be due to the presence of another substance, spasm-producing in nature. Both substances are theoretically present in voluntary muscle from which they get into the circulation after injection of epinephrin or after exercise. Fahrenkamp and Schneider¹² fail to find evidence that the voluntary or cardiac muscles possess a hormone. In comparative studies on man of the extract of heart muscle ("Carnigen"), which is albumin-, histamin- and epinephrin-free, and the extract of voluntary muscle, they find that both possess the same action. They slow the ventricular rate both in fibrillating hearts and in those with sinus rhythm when given orally to patients under the influence of digitalis. In patients with high blood-pressure they cause a fall of from 10 to 30 millimeters of mercury, whereas in those without a high pressure there is a transitory rise of about the same amount. Both extracts administered either orally or intravenously control recurring seizures of angina pectoris, produce sleep in those hypertensives who are unable to sleep, but do at times produce symptoms of angina pectoris in patients under the influence of digitalis.

Fahrenkamp and Schneider recommend 15 to 60 drops of the extract daily by mouth in cases of moderate severity and from 1 to 2 cubic centimeters intravenously in severe angina.

Radiotherapy, too, claims its share of success in the treatment of angina pectoris. Nemours-Auguste¹³ reports thirty-one cures in fifty-four angina pectoris patients who used radiotherapy as a last resort after trying in vain every other remedy that promised relief. The beneficial results, produced perhaps by blocking the sympathetic pathways through the paravertebral ganglia, are most evident in those suffering with arrhythmias, extrasystoles, irritable hearts and paroxysmal tachycardia.

Of interest is Ziskin's¹⁴ administration of thyroid extract to a myxedema patient with anginal attacks. Administration of 3 grains daily produced complete disappearance of the attacks. He warns that this treatment should be used only in those who have well-defined hypofunction of the thyroid.

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QUINIDINE THERAPY

In auricular fibrillation, when the integrity of the circulation is restored with digitalis one is faced with two alternatives, according to Stroud and Reisinger;¹ either continuance of the maintenance dose of digitalis over an unlimited period of time or an attempt to restore normal sinus rhythm by the use of quinidine sulphate. Quinidine may be of value in multiple premature contractions, rheumatic or non-rheumatic in origin, in auricular flutter if digitalization is not successful, in fibrillation produced by digitalis, in fibrillation which responds rapidly to digitalis therapy and rest, in fibrillation in which there is little evidence of congestive circulatory failure and finally in fibrillation in which the fluoroscope demonstrates vigorously pulsating ventricles. The average procedure with quinidine sulphate on the G. W. Norris Service at the Pennsylvania Hospital is outlined below. The patient to be treated is of average size: he gets a maintenance dose of digitalis. The galvanometer is near at hand: when it indicates that the sinus rhythm is restored, quinidine is stopped.

			A.M.	P.M.	A.M.	
24 hrs.	Quinidine Sulphate—3 grains at		6-10	-2-6	-10-2	18 grains
48 "	" " —3 "	"	6-10	-2-6	-10-2	36 "
72 "	" " —6 "	"	6-10	-2-6	-10-2	72 "
96 "	" " —6 "	"	6-10	-2-6	-10-2	108 "
120 "	" " —9 "	"	6-10	-2-6	-10-2	162 "
144 "	" " —9 "	"	6-10	-2-6	-10-2	216 "

If unsuccessful after seven- to ten-day interval, the above procedure should be repeated. As is well known (Wright²) quinidine abolishes the circus movement in the auricles by (1) lowering the rate of impulse formation in the sino-auricular node, (2) depressing conductivity in the auricles, ventricles, and bundle of His, (3) producing partial paralysis of the vagus, and (4) lengthening the refractory period of the heart muscle. When the circus movement reaches the heart muscle the refractory period, when sufficiently lengthened, predominates, and the wave is arrested and normal

rhythm is reestablished. If, however, the conducting factor predominates, the circus continues, but is slowed down (Lewis).

The results of seven years of treatment with quinidine sulphate have been reported by Wolff and White.³ Quinidine sulphate was responsible in abolishing the circus movement in about 67 per cent. of the 133 cases of established auricular fibrillation. Harris,⁴ in treating forty-three consecutive cases of chronic auricular fibrillation with quinidine, was successful in reestablishing normal rhythm in 60 per cent. of cases. The hyperthyroid cases reacted more readily to the drug than did the hypertensive and arteriosclerotic cases. The mentioned percentage rises to 81.8 in those cases in which fibrillation had lasted for less than a month. The follow-up study of an early series of cases showed that normal rhythm has lasted for six to seven years in 11.7 per cent. of the patients. They claim digitalis as superior to quinidine in treating auricular flutter. These men emphasize, as do Stroud and others, that with predigitalization and maximal dehydration and salt reduction, normal rhythm is obtained with smaller doses of quinidine.

In the postoperative treatment of auricular fibrillation due to thyroid disease startling results have been published by Hurxthal.⁵ In fifty-nine such cases, digitalis slowed the pulse, but was no more capable of converting the rhythm back to normal than was no medication at all. Quinidine restored the normal rhythm in every case. Since most of the cases revert spontaneously to a normal rhythm it is difficult to evaluate quinidine. Hurxthal feels that this drug should be used when the fibrillation persists three or four days after the operation.

Morawitz and Hochrein⁶ claim to stave off sudden death by using quinidine alkaloid in doses of 0.1 gm. twice a day. Such deaths, probably due to sudden inception of ventricular fibrillation, are forewarned by the electrocardiogram. The changes indicative of bundle branch block and arborization block, as well as possibly the inversion of T waves in two or more leads and the occurrence of upward convexity of the S-T line are warning signals. Frequent premature ectopic beats, especially in elderly persons with chronic myocardial degeneration, are also of prognostic value.

Most observers admit the danger accompanying quinidine therapy. Olshausen⁷ finds, in contrast to the prevailing opinion, no

contra-indications to its use. Neither a cardiac defect nor its extent, neither combined defects nor giant hearts, neither advanced age nor even decompensation contra-indicates its intelligent use. It should be given by all means when death is imminent and when digitalis is of no avail. The danger is an indirect one—that of dislodging of auricular clots when auricular fibrillation ceases. Wolff and White³ state that, in addition to liability to embolism, quinidine produces a direct toxic effect upon the cardiac muscle. For this reason large doses should be avoided. Davis and Sprague⁸ claim on electrocardiographic evidence that some of the sudden deaths are due to the very thing that quinidine is reputed to suppress—ventricular fibrillation. The reason that this phenomenon is not more observed is that death comes on so rapidly after its inception.

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ELECTROCARDIOGRAPHY

A sharp definition of what constitutes a normal electrocardiographic tracing is still a matter of conjecture. There is difficulty, as Wolferth¹ remarks, in determining how much significance to ascribe to slightly aberrant curves. Physiological reactions as, for example, those following exercise (Messerle²), and those following exposure to cold (Otto³), result in temporary electrocardiographic deviations.

As a result of exercise, according to Wright,⁴ the diastolic pause is shortened and the amplitude of the T wave is increased. The mode of production of the T wave still remains unexplained.

As pointed out by Wright,⁴ one would expect the T wave to be deflected downward instead of upward. The T wave is possibly the persistence at the base of the excitation process which spreads in the ventricle from apex to base. In diabetic coma there are wave changes, according to Lauter and Baumann⁵ and Taterka.⁶ The latter reports reduction in the height of the T wave, not in diabetics, but solely in cases of diabetes which have gone on to coma. The cause of the change was ascribed to myocardial damage resulting from acidosis. From the fact that a T wave, abnormal in form, direction, or reaction to exercise in Leads I and II, is evidence of serious cardiac damage which may lead to unexpected death (Wright⁴), it has been concluded that the T wave is related to the functional state at the base of the ventricles. With aortic regurgitation, gummatata or other cardiopathies involving this portion of the heart there are T wave abnormalities. Toxic doses of digitalis invert the T wave. The daily maintenance dose of digitalis was determined in electrocardiographic studies of the T wave and P-R interval (conduction time of the bundle of His) by Bromer and Blumgart.⁷ They found by this means that the daily maintenance dose is 23.5 minims of the tincture and that changes in the T wave may be used as a quantitative index of the amount of digitalis effective within the body. The T wave and R-T interval changes associated with acute rheumatic pericarditis with effusion are probably caused by a complicating myocardial damage. This assumption is more or less substantiated by the observation by Porte and Pardee⁸ that similar alterations in the T wave are found in coronary artery narrowing.

The fact that quite dissimilar pathological changes may affect the T wave similarly is not at all discordant with our present understanding of this wave, for it is likely that location of the damage is of more importance than the damaging agent. There are marked differences in the T wave findings in lesions of the right and of the left ventricles, say Barnes and Whitten⁹ in their study of 177 cases. There appears to be a definite correlation between site of lesion and T wave changes. When the strain due to pathological changes

contra-indications to its use. Neither a cardiac defect nor its extent, neither combined defects nor giant hearts, neither advanced age nor even decompensation contra-indicates its intelligent use. It should be given by all means when death is imminent and when digitalis is of no avail. The danger is an indirect one—that of dislodging of auricular clots when auricular fibrillation ceases. Wolff and White³ state that, in addition to liability to embolism, quinidine produces a direct toxic effect upon the cardiac muscle. For this reason large doses should be avoided. Davis and Sprague⁸ claim on electrocardiographic evidence that some of the sudden deaths are due to the very thing that quinidine is reputed to suppress—ventricular fibrillation. The reason that this phenomenon is not more observed is that death comes on so rapidly after its inception.

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was predominantly on the left ventricle there was inversion of the T waves in Lead I in 84 per cent. of cases. In the 7 per cent. of this group showing T wave inversion in Leads II and III, there was infarction of the left ventricle in all but seven cases. With the right ventricle bearing the brunt of the load the T waves were inverted in Leads II and III in 83 per cent. of cases. T wave changes indicate not only myocardial damage but also, according to Juster and Pardee,¹⁰ serious coronary artery involvement. Necropsies on ten of the fifty cases of syphilitic aortitis, two-thirds of which had aortic insufficiency, revealed that T wave changes were associated with encroachment of the syphilitic disease upon the coronary arteries at their origins from the aorta.

The P wave, which represents the passage of the excitation process over the auricle, is changed in a variety of conditions (Wright⁴). The extent of the wave is a reliable guide to the functional activity of the auricular muscle. Hypertrophy of the left auricle, as occurs in mitral stenosis, is associated with P wave prominence or bifurcation. In auricular fibrillation, if the cardiac impulse arises in an abnormal focus, the P wave is altered or inverted. If the proper spread of the excitation process is hampered by a hypertrophied or damaged muscle there is a prolongation of the P wave. An increase in the duration of the P-R interval to more than 0.2 second is definite evidence of delayed conductivity in the bundle of His.

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OPERATIVE RISK IN CARDIAC DISEASE

The presence of cardiac disease has always been considered a factor of great importance in determining the advisability of major operative procedures and in contributing to operative and postoperative mortality. In view of the frequency with which this problem must be met in a practical manner, studies such as that recently reported by Levine⁵⁶ are of vital interest and significance. This study consists of an analysis of the results of 494 operations of various types, under both local and general anesthesia, upon 414 patients with various forms of heart disease.

The total mortality was 12 per cent. in the group in which local anesthesia was employed and 12.1 per cent. in the general anesthesia series. The unexpected mortality, that which was perhaps not dependent primarily upon the surgical condition, was 6.3 per cent. The detailed statistics in patients suffering with certain of the more serious cardiac affections are highly illuminating. There were ninety-nine operations in the presence of auricular fibrillation, with three deaths; nineteen patients with auricular flutter were included, with one death. In thirty-five operations upon individuals with angina pectoris there were three deaths. In the series of 414 patients, thirty-eight presented manifestations of congestive heart failure which was present either before or after operation. There were three deaths in this group (10.2 per cent.). The author expresses the opinion that, as is to be expected, congestive failure developing after operation must be considered in a more serious light, prognostically, than that present prior to operation. The conclusion that must be drawn from this critical analysis of a large series of cases would appear to be that chronic cardiac disease, even though advanced in degree, does not add seriously to operative and postoperative mortality in expert hands. Naturally, proper pre- and postoperative treatment is essential as well as careful management of the operative procedure so that trauma and shock are reduced to a minimum and as little strain as possible is thrown upon the cardiovascular system.

The data in the case of more acute cardiac disorders are, however, quite different. In operations upon twenty patients suffering with coronary artery thrombosis there were eight deaths; only one out of five patients recovered following operation during an acute attack. Evidently operative procedures attempted during the acute stages of cardiac disease, before the circulatory system has had an opportunity to readjust itself to suddenly altered conditions, are attended with grave danger.

The effect of nephritis, occurring in association with cardiac disease, is interesting. In sixty-one operations upon fifty-five patients with nephritis there were eight deaths (14.8 per cent.); this is in rather sharp contrast to the relatively low mortality in non-nephritics, twenty deaths in 433 operations upon 359 individuals (4.9 per cent.). There was no apparent relationship between the blood-pressure level and the mortality rate. Clearly, renal complications add to the operative hazard in patients with cardiac disease, but perhaps no more so than in otherwise normal individuals.

In this connection the observations of Lahey⁵⁷ are of interest. He believes that thyrotoxicosis, *per se*, does not have a destructive influence on the myocardium and that partial thyroidectomy can in most instances be performed, even in the presence of congestive heart failure, with but little increased operative risk. In fact, improvement in the condition of the circulation usually follows such surgical procedures because of the removal of the extra load incident to the tachycardia and increased velocity of blood flow associated with the thyrotoxic state.

The realization is rapidly growing that in conditions demanding surgical intervention, as well as in pregnancy, the presence of chronic heart disease does not add greatly to the expected mortality. Care must necessarily be exercised, particularly in pre- and post-operative management. Operation in the presence of acute cardiac disease should, if possible, be delayed until readjustment of the circulation can take place, at which time it may be performed with reasonable security.

CONGESTIVE HEART FAILURE

Many phases of certain clinical problems associated with congestive heart failure remain shrouded in mystery despite numerous

physiologic, clinical and pharmacologic studies. One of the most important of these problems is the significance and mode of production of edema.

There is as yet no complete agreement among physiologists as to the exact pathologic physiology of cardiac edema. One phase of this problem has received comparatively little investigation, namely the effect of edema upon the efficiency of the circulation and upon metabolic activities in the tissues. Harrison and Pilcher have made an intensive study of the effect of edema on tissue oxygen utilization which throws new light upon this extremely common clinical condition. It was shown that the utilization of oxygen by edematous tissues is less than normal, the degree of diminution being roughly proportional to the amount of edema and independent of the condition of the circulation. The decreased oxygen utilization is believed to be due not to diminished oxygen consumption, but to an increased rate of blood flow through the edematous tissues.

This observation is of considerable clinical significance in congestive heart failure. All of the presented evidence indicates that the presence of edema throws an additional burden upon an already embarrassed circulatory mechanism. In the words of the authors, "It appears that edema *per se* may constitute a danger for the heart. Assuming its occurrence, the increased blood flow through the edematous tissues would be almost certain to cause a local increase in capillary and venous pressure. But, a rise in capillary pressure tends, *ceteris paribus*, to produce edema. Thus a vicious cycle would be formed, the edema tending to increase in amount, unless restricted by other factors.

"When only a small proportion of the body tissues is edematous, the effect on the general circulation would probably be small. But when a large proportion, such as all of both lower extremities, is edematous, it seems likely that the circulation to the body as a whole would be seriously affected. Compensation might be affected in one or both of two ways. Either (1) the blood flow through the edematous tissues being increased and the minute output of the heart remaining constant, the remainder of the body may receive less than the normal quota of blood or (2) the blood flow through the edematous portions being increased and the remainder of the body receiving its normal quota of blood, the minute output of

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The data in the case of more acute cardiac disorders are, however, quite different. In operations upon twenty patients suffering with coronary artery thrombosis there were eight deaths; only one out of five patients recovered following operation during an acute attack. Evidently operative procedures attempted during the acute stages of cardiac disease, before the circulatory system has had an opportunity to readjust itself to suddenly altered conditions, are attended with grave danger.

The effect of nephritis, occurring in association with cardiac disease, is interesting. In sixty-one operations upon fifty-five patients with nephritis there were eight deaths (14.8 per cent.); this is in rather sharp contrast to the relatively low mortality in non-nephritics, twenty deaths in 433 operations upon 359 individuals (4.9 per cent.). There was no apparent relationship between the blood-pressure level and the mortality rate. Clearly, renal complications add to the operative hazard in patients with cardiac disease, but perhaps no more so than in otherwise normal individuals.

In this connection the observations of Lahey⁵⁷ are of interest. He believes that thyrotoxicosis, *per se*, does not have a destructive influence on the myocardium and that partial thyroidectomy can in most instances be performed, even in the presence of congestive heart failure, with but little increased operative risk. In fact, improvement in the condition of the circulation usually follows such surgical procedures because of the removal of the extra load incident to the tachycardia and increased velocity of blood flow associated with the thyrotoxic state.

The realization is rapidly growing that in conditions demanding surgical intervention, as well as in pregnancy, the presence of chronic heart disease does not add greatly to the expected mortality. Care must necessarily be exercised, particularly in pre- and post-operative management. Operation in the presence of acute cardiac disease should, if possible, be delayed until readjustment of the circulation can take place, at which time it may be performed with reasonable security.

CONGESTIVE HEART FAILURE

Many phases of certain clinical problems associated with congestive heart failure remain shrouded in mystery despite numerous

physiologic, clinical and pharmacologic studies. One of the most important of these problems is the significance and mode of production of edema.

There is as yet no complete agreement among physiologists as to the exact pathologic physiology of cardiac edema. One phase of this problem has received comparatively little investigation, namely the effect of edema upon the efficiency of the circulation and upon metabolic activities in the tissues. Harrison and Pilcher have made an intensive study of the effect of edema on tissue oxygen utilization which throws new light upon this extremely common clinical condition. It was shown that the utilization of oxygen by edematous tissues is less than normal, the degree of diminution being roughly proportional to the amount of edema and independent of the condition of the circulation. The decreased oxygen utilization is believed to be due not to diminished oxygen consumption, but to an increased rate of blood flow through the edematous tissues.

This observation is of considerable clinical significance in congestive heart failure. All of the presented evidence indicates that the presence of edema throws an additional burden upon an already embarrassed circulatory mechanism. In the words of the authors, "It appears that edema *per se* may constitute a danger for the heart. Assuming its occurrence, the increased blood flow through the edematous tissues would be almost certain to cause a local increase in capillary and venous pressure. But, a rise in capillary pressure tends, *ceteris paribus*, to produce edema. Thus a vicious cycle would be formed, the edema tending to increase in amount, unless restricted by other factors.

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the heart must be increased. In the first case, compensation has been established at the expense of the vital tissues of the body; in the second instance, an additional load has been thrust on the already overburdened heart."

In view of this evidence that edema associated with cardiac disease tends, *per se*, to increase the severity of the conditions underlying the production of the edema, it is obvious that every effort should be made to combat it for, as stated by the authors, "in so doing, we are treating not only a symptom but a link in that chain of events which constitutes the vicious cycles of heart failure." Stewart advocates the addition of another drug to the long list of those used for the relief of cardiac edema. Theocalcin (theobromine-calcium salicylate) has been rather extensively used in the treatment of arterial hypertension. Selig was the first to publish reports of the diuretic effect of this drug. Stewart administered theocalcin in doses of 1.0 to 1.5 gm. three times a day to sixteen patients with congestive heart failure. Diuresis occurred in eleven cases (69 per cent.). No such effect was noted in one patient without manifestations of congestive heart failure, and in another with edema due to nephritis.

In some cases theocalcin was effective as a diuretic after other drugs, including digitalis, theocin, diuretin and novasurol had failed, and was clearly the most effective diuretic used in the treatment of the reported series of patients. It may be administered without untoward results as long as diuresis lasts, manifestations of gastric irritation being observed but rarely, and only when diuresis had ceased or had not occurred. Digitalis of course cannot be replaced by theocalcin in the treatment of congestive heart failure, but it appears to be a valuable addition to the measures used in combating the edema which has been demonstrated to seriously impair circulatory efficiency under most favorable conditions.

The efficacy of digitalis in myocardial failure and in disturbances of cardiac rhythm has long been recognized. Concerning its mode of action in relieving the manifestations of heart failure there is, however, considerable difference of opinion. This subject is of the greatest practical importance inasmuch as, when completely understood, it will not only explain the reasons for the failure of digitalis in certain patients with congestive heart failure but will

enable us to choose more intelligently those cases suitable for digitalis therapy. A great deal of interesting work has recently been done in this connection.

In 1908, Tigerstedt found that under digitalis administration the cardiac output was decreased in normal rabbits and increased in rabbits with circulatory impairment. More recently Harrison and Leonard, and Cohn and Stewart demonstrated a diminution in cardiac output and in the size of the hearts of digitalized dogs, these authors, however, differing in their interpretation of these changes. Dock and Tainter criticize conclusions drawn from previous investigations on the ground that all of the factors involved in the action of digitalis were not considered. They found that the administration of a full therapeutic dose of digitalis was followed by a fall of venous pressure associated with a decrease in cardiac output. The conclusion was reached that the change in blood flow was the result of peripheral and not cardiac actions of the drug, being in agreement with the general belief that normal cardiac output is dependent largely upon the venous return.

Ringer and Altschule analyze the factors which constitute the reserve functional capacity of the circulation as follows:

(1) The ventricular output (stroke volume).

(2) The ventricular rate.

(3) Other factors which reside in the blood and tissues; the efficiency of the respiratory function of the circulation, as measured by the arterial-venous oxygen content difference, serves as index of the functional efficiency of these factors.

(4) The ability of the muscles to work under an oxygen deficit which is removed by the circulation after effort has subsided.

In compensated heart disease the minute volume of circulating blood (heart rate x stroke volume) is within normal limits whereas in decompensated heart disease it is diminished, due largely to a decrease in the stroke volume. These authors believe that the effectiveness of digitalis, which apparently does not restore the minute volume to normal, depends upon a shifting of the burden from one cardiac reserve factor to another, i.e., from increased ventricular rate and low stroke volume to slow rate and increased stroke volume. This is obviously not the only factor involved but is one of distinct importance.

There can be little doubt that the heart contracts with increased efficiency after therapeutic doses of digitalis. It is becoming, moreover, increasingly apparent that the action of digitalis varies with the functional state of the circulation in determining cardiac output. In the normal animal, and perhaps in man, there is a reduction following digitalis administration. In the presence of congestive heart failure, however, digitalis seems to tend to increase cardiac output and to elevate the venous pressure to the normal level. These observations illustrate the fact, all too frequently forgotten or overlooked, that the actions of drugs upon healthy organs may be quite different from their effect upon diseased or functionally deranged structures.

DIGITALIS THERAPY

In their treatment of auricular fibrillation, Stroud and Reisinger¹ comment upon the uselessness of small doses of digitalis. Only when therapeutic concentration is reached, as determined by change in apical rate or by appearance of nausea or vomiting, is there real benefit. In the average case, 2 minims (5 drops) of the tincture or 1/5 grain of powdered leaf per pound of body weight, produces therapeutic concentration. The average procedure with digitalis in auricular fibrillation on the G. W. Norris Service at the Pennsylvania Hospital follows. The patient to be treated weighs 150 pounds (estimated free of edema).

		H.R.	P.R.
24 hrs.	{ 60 minims, 6 grains 30 minims, 4th hour, while awake, (4 doses) Total 180 minims, 18 grains }	180-200	60-110
48 hrs.	{ 30 minims, 4th hour (4 doses) Total 300 minims, 30 grains }	100-120	68-112
72 hrs.	{ 20 minims, 4th hour (4 doses) Total 380 minims, 38 grains }	80-100	70-100
96 hrs.	{ 10 minims t.i.d. (3 doses) Total 410 minims, 41 grains }	70-80	70-80
(Daily maintenance dose, 20 to 30 minims)			

The cardiac conditions calling for an immediate cessation of administration of digitalis for at least twenty-four hours have been

reiterated by Stroud and Bromer.² They are, namely, extrasystoles, coupled rhythm, partial auriculo-ventricular heart block, complete heart block, paroxysmal tachycardia, and regular sinus rhythm becoming irregular or intermittent. In treating a cardiac patient for the first time it is important, they urge, to be familiar with previous digitalis therapy during the past fifteen days, for, after stopping its administration, its effects persist for that length of time (Pardee). When there are no scales to weigh a patient, his size serves as a safe index to the amount of digitalis necessary for therapeutic concentration. A person of small size needs about 30 grains (2.0 Gm.) of powdered leaves or 300 minimis of tincture, a person of medium size requires about 33.75 grains (2.25 Gm.) of leaves or 337.5 minimis of tincture, while a large person must have 37.50 grains (2.5 Gm.) of leaves or 375 minimis of tincture. There is no need of rapid digitalization when decompensation is slight. A dose of from 1.5 to 3.0 grains (0.1 to 0.2 Gm.) of powdered leaves or of 15 to 30 minimis of tincture (40 to 80 drops) given three or four times a day produces digitalization in from three to seven days.

Stewart³ feels that administration of digitalis is far from a simple problem. Wisdom in the use of digitalis has to be based in large part upon the etiology of the cardiac condition. The drug is inadequate more often in the failure of an arteriosclerotic than of a rheumatic heart perhaps because of difference in impairment of its blood supply. Or perhaps the fault lies in the digitalis, according to Cloetta.⁴ Aside from the active components, such as the glucosides, there are inactive substances in the leaves, such as salts and saponins. Among the salts, the main constituent is potassium, which counteracts the activity of the glucosides and their genins in extracts made from the leaves. On the other hand, there are saponins which may be considered as accelerators of the glucosidal action. Thus, according to its potassium content, its saponin content and again, according to its glucosidal content, digitalis may vary widely in action. It must be remembered, too, that value and ultimate prognosis of digitalis are dependent upon the site of the cardiac lesion. Moon,⁵ in his St. Cyres lecture, states that if the disease is confined to the auricles the outlook is more promising than if the ventricles too are involved. If the ventricles are affected, lesions of the apex

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CONTRA-INDICATION OF DIGITALIS THERAPY IN LOBAR PNEUMONIA AND DIPHTHERIA

In contrast to the views of such observers as Burrage and White of Massachusetts General Hospital, Phillips and Bliss of Fort Riley, Kansas, and others, who favor the use of digitalis in pneumonia, Niles and Wyckoff¹ have come to the conclusion that results do not justify its continued use. Some men have heretofore opposed its use or have expressed little enthusiasm for it—these are notably Sir James Mackenzie, Hare, Brunton and Stuart Hart. In their study at the Bellevue Hospital in New York, Niles and Wyckoff divided all the admissions with lobar pneumonia into four groups: those (Class A) who were to have neither serum nor digitalis; those (Class B) who were to be given serum only; those (Class C) who were to receive digitalis only; and those (Class D) who were to be given both serum and digitalis. One of their first observations was in regard to potency of the well-known commercial brand of digitalis which they were using. The potency, according to the cat method of assay, was twice that indicated by the manufacturer's statement (Wyckoff, Gold and Travell²). In the group of patients upon whom this potent digitalis had been used there was a mortality 13.5 per cent. higher than that of the control group, or, stated in another way, for every 100 control patients who died, there died 140 patients treated with this double-strength brand of digitalis.

or of the interventricular septum are of more serious consequence than those elsewhere.

Cloetta⁴ experimented with rabbits whose aortic valves had been damaged, in an effort to find out the effect of digitalis in such a condition. He found that the animals treated regularly with digitalis developed much less hypertrophy and dilation of the heart and had greater cardiac reserve power than the untreated controls. This has led him to the opinion, in contrast with the present clinical teaching, that early cases of endocarditis likely to develop valvular defects should receive digitalis therapy.

Calcium as an adjuvant to digitalis may possibly be of promise. Billingheimer⁶ found that with the injection of a 10 per cent. solution of calcium chlorid intravenously there is a slowing of the pulse which reaches its minimum in a half hour and persists for four to five hours. He quotes the work of Sovadina *et al.*, and others, in support of his view that digitalis is much more effective when supplemented with calcium. Sovadina *et al.* used a mixture of 10 per cent. calcium chlorid solution and 1 to 3 cubic centimeters of digalen at twelve- to twenty-four-hour intervals in the treatment of croupous pneumonia with good results. Stewart⁷ has failed entirely to substantiate these views.

Trendelenburg⁸ went rather carefully into the comparative value of various remedies in their ability to relieve true cardiac insufficiency. Digitalis and strophanthus are still unrivaled, perhaps because of absence of constrictor effect upon the peripheral blood-vessels, differing in this regard from adrenalin and ephedrin, whose stimulating effect upon the heart is overcome by peripheral resistance. Cardiazol, coramin and hexeton they found useless. Donovan and Davis⁹ have had satisfactory results from ouabain, a crystallized form of strophanthus of uniform strength and action. It not only stimulates tonus far better than digitalis (Vaquez) but also has fewer toxic effects. It is probably the best emergency heart stimulant when given intravenously in a dose of 1/240 grain.

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As a consequence, a standardized, non-commercial digitalis was obtained and used for the subsequent study. Over a period of two years, for every 100 cases in the control group that died, there were 122 fatalities in the digitalis-treated group. Regarding the factor or virulence of the specific pneumococcus types—in all types except Type II—the mortality of the digitalis-treated cases was higher than that of their controls. Cases with positive blood culture and septic complications such as empyema, endocarditis, lung abscess and suppurative arthritis do not influence the relative mortality of the control and digitalis-treated patients.

Hare,³ in commenting upon this work, states that under some circumstances digitalis is positively contra-indicated in pneumonia, as, for example, in those instances where partial heart block seems to be a cardiac condition. In instances where the general condition of the patient is manifestly one of grave toxemia, the question as to whether digitalis should or should not be used may be answered in the negative in a fair proportion of cases: an electrocardiogram may show digitalis to be contra-indicated. The electrocardiogram has shown, according to Stecher,⁴ that digitalis is definitely contra-indicated in diphtheria, as has been generally maintained by pediatricians. Stecher reports nineteen cases of heart block occurring in patients with diphtheria all of whom were under twenty years of age. All had received early administration of antitoxin. Death occurred in every one of these cases of heart block within ten days.

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DIET IN TREATMENT OF TUBERCULOSIS

The European literature contains many references to the dietary treatment of tuberculosis. The régime which appears to be most popularly employed is embodied in the Gerson-Sauerbruch-Her-

mannsdorfer diet. This is essentially an alkaline, salt-poor diet, high in vitamins A, B, and D, consisting largely of raw fruits, fresh vegetables, large amounts of fluid (milk and soups), phosphorus, calcium salts, and cod-liver oil. As is true of practically all methods of treatment of this disease, there is a remarkable variation in the results obtained by different investigators.

Sachs believes that the Gerson diet is of no value in pulmonary tuberculosis, and Harms and Grünwald state that they observed no symptomatic, objective or laboratory evidence of improvement. They conclude that the régime is not only not helpful, but may be distinctly harmful in patients with pulmonary tuberculosis. Starcke feels that the Gerson diet is of no value in the treatment of tuberculosis during childhood and adolescence.

On the other hand, Wolff-Eisner reports encouraging results. Mecklenburg is of the opinion that a favorable influence is exerted upon organs which are disturbed functionally, but that no curative effect has been noted upon the tuberculous lesions themselves. Pöhlmann believes that good results may be obtained in pulmonary and laryngeal tuberculosis by means of this dietary régime, but warns against its over-evaluation. Clairmont and Dimtza report that nearly all patients suffering with tuberculous lesions of the skin and fistula in ano are benefited by this mode of therapy. In view of such contradictory reports it is evident that the many enthusiastic claims made for the alkaline, salt-free diet, and its various modifications in the treatment of tuberculosis must be considered critically and not viewed with undue optimism.

The realization of the essential part played by vitamin D in normal and pathological calcification naturally led to investigation of its effect upon tuberculous processes, calcification of which is generally believed to be indicative of quiescence or healing. Here again the evidence is highly contradictory in nature and its interpretation extremely difficult. Grant believes that the addition of vitamin D to a previously adequate diet increases the resistance to tuberculosis. He concludes that a disturbance of vitamin C, vitamin D and calcium balance perhaps decreases the resistance to tuberculous infection. Similarly, Pfannenstiel and Scharlan make the observation that the administration of vitamin A, B or D singly has no effect upon the tuberculous process. Vitamin B (yeast) and

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mixed with some agent, probably trypsin, which inhibits its glyco-
protein effect. The studies of Karelitz, Cohen and Leader are of
interest in this connection. They found that blood inhibits the
action of insulin when injected with it, intramuscularly or subcu-
taneously, into rabbits. The blood of diabetics is more potent in
this respect than that of normal individuals, and the cells possess
this property to a more marked degree than the plasma. Blood taken
from patients with some infectious process is likewise more effective
than normal blood. It appears that the process of insulin inac-
tivation requires time and does not occur if the blood and insulin
are injected intravenously. It is suggested by the authors that the
agent responsible for this phenomenon may be trypsin or some tryp-
sin-like substance, the inhibitory action of which varies in different
individuals and under different conditions and which may be re-
sponsible for the marked variation in the response to insulin noted
in certain diabetic patients. Schmidt found that insulin is inac-
tivated to a marked degree by liver tissue and to a lesser extent
by kidney. He likewise believes that increased inactivation by pro-
teolytic ferment may be the basis for the resistance to insulin ex-
hibited by certain diabetics. This not unattractive hypothesis has
some experimental and clinical support, and, if further substantiated,
may clarify many of the poorly understood aspects of diabetes.

As long ago as 1917, Joslin, Bloor and Gray showed that in
diabetics there is a definite increase in blood lipoids, the degree of
lipidemia bearing a direct, although not quantitative relation to
the severity of the disease. Since that time investigations of lipid
metabolism have in the main corroborated these observations. Rab-
binowitch found that the cholesterol content of the blood plasma
is a more direct index of the course of the diabetic condition in any
given individual than is the blood sugar. In a subsequent report of

the necessity for an adequate amount and proper balance of vitamins and inorganic elements for the maintenance of normal metabolism and proper nutrition, so essential in tuberculosis, the addition of these elements to the dietary régime is unwarranted and rests upon no sound physiologic basis. Our knowledge of the clinical and pathologic manifestations of mild grades of hypervitaminosis is as yet too limited to enable us to realize its possible dangers, but the injudicious administration of these potent agents in excessive amounts is capable of producing serious effects which cannot be disregarded.

DIABETES MELLITUS

With the introduction of insulin into the practical treatment of diabetes mellitus it was naturally hoped that the mortality from this condition would be appreciably decreased. It is difficult to realize why this expectation has not been realized. Excessive consumption of carbohydrates has frequently been mentioned as an important predisposing factor in the etiology of diabetes. This hypothesis has not been supported by either clinical or experimental evidence and appears to be invalidated by the statistical study reported by Mills. This study consists of a compilation of data regarding the sugar consumption and diabetic mortality in various countries. There is no apparent relationship between the death rate from diabetes and the consumption of sugar as indicated by these statistics. Obviously, investigations of this nature cannot be accepted as conclusive, but they serve to emphasize the fact, too often forgotten, that the etiology of diabetes is still unknown.

One of the factors which has puzzled investigators of the pathological physiology of diabetes mellitus is the observation that the tissues of individuals who have succumbed to that disease apparently contain much more insulin than is required to maintain carbohydrate metabolism at a normal level. The logical explanation for this seemingly paradoxical finding is that the insulin present in the tissues of these individuals is inactivated in some manner and is thus prevented from exerting its effect upon carbohydrate metabolism. Epstein accordingly proposed the hypothesis that diabetes is due, not to a failure of the pancreas to elaborate sufficient insulin, but rather to some mechanism whereby the insulin is brought in

vitamin D (viosterol) given in combination exert a favorable influence which is more pronounced if vitamin A (cod-liver oil) is added. Menschel reports distinct improvement in a series of patients treated by routine methods supplemented by the administration of viosterol. Fever was reduced, weight increased, the quantity of sputum diminished and the tendency to hemorrhage lessened. Improvement was noted in bone, skin and laryngeal lesions; anemia, however, was not influenced. He believes that viosterol exhibits exudation and favors healing of the tuberculous process. McConkey states that the routine use of cod-liver oil and tomato juice in intestinal tuberculosis is a valuable measure, at least as effective as heliotherapy. A palatable preparation may be made by floating $\frac{1}{2}$ ounce of cod-liver oil on 3 ounces of tomato juice, serving it ice-cold after meals. The juice of an average-sized orange may be substituted for the tomato juice.

Spies and Glover warn against the widespread use of viosterol in the treatment of tuberculosis, emphasizing the potential danger of such a procedure. They state, corroborating the work of previous investigators, that calcification of tuberculous lesions by this means is merely a manifestation of metastatic calcification which may occur in predisposed tissues, particularly those undergoing necrosis. Furthermore, calcific deposits are prone to occur in healthy tissues, particularly in the kidney, producing marked renal damage with manifestations of renal insufficiency. As Hess has pointed out, hypercalcemia and metastatic calcification, with their attending deleterious effects, must be considered to fall within the realm of toxicology rather than pharmacology. However, at the present time there appears to be no justification for the employment of vitamin D in the hope of influencing the progress of the tuberculous process. So far as can be determined, this agent exerts a specific effect only in rickets and allied disorders such as osteomalacia and infantile tetany, and has no influence upon disturbances of calcification other than those dependent upon vitamin D deficiency. Pulmonary tuberculosis, in the light of modern studies, is associated with no alteration in mineral metabolism; it has been clearly demonstrated that, although calcified lesions are usually inactive they are not invariably so, and it is probable that calcification follows rather than precedes healing. It appears that, apart from

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affords some insight into the susceptibility of diabetic patients to the development of this serious complication with its dreaded sequel, coma.

A recent study of the cholesterol of the blood of diabetic children by Hunt and White is of particular importance because of the peculiar liability of children to acute disturbances of fat metabolism and to the development of diabetic coma. Observations made upon 110 diabetic children over a period of four years revealed certain points of similarity and difference between the lipoid metabolism of children and that of adults. It was found that although there was no close correspondence between glycosuria, glycemia and the level of blood cholesterol, hypercholesterolemia occurs very infrequently in uncomplicated diabetes in children. Acidosis was not invariably associated with an increase in plasma cholesterol but hypercholesterolemia (258-1220 milligrams per cent.) was present in every case of coma. The severity of the coma bore no relation to the degree of elevation of the cholesterol and none of the chemical features could be accepted as indicative of the prognosis in diabetic coma.

Overnutrition was found to be accompanied by an increase in cholesterol. The observation that only 46 per cent. of the patients with arteriosclerosis showed such increases is of significance in view of the reputed etiological rôle of hypercholesterolemia in arteriosclerosis and the almost constant association of these conditions in adult diabetics. Further studies in this direction may throw some light upon the much disputed point as to whether hyperglycemia or hypercholesterolemia is the dominant factor in the development of arteriosclerosis in diabetes.

As the authors state, "With this amount of data available on diabetic children, we cannot say whether the prognosis of complications or life depends upon the height of the cholesterol in the blood. Our data furnish what we regard as new links in the chain of evidence rather than as ultimate conclusions." It is becoming increasingly apparent that the complex nature of the metabolic disturbance in diabetes mellitus necessitates the investigation of all phases of body metabolism and that, from a clinical standpoint, the primary error in carbohydrate metabolism may be overshadowed in importance by manifestations of associated disturbances in the metabolism of lipids.

A case reported by Griffiths illustrates one of the difficulties encountered in the management of patients with diabetes if adequate laboratory studies are not obtained. A woman, fifty-five years of age, had been known to be suffering with diabetes of rather mild degree, with glycosuria and moderate hyperglycemia. Following the development of a suppurative process in one hand her general condition suddenly became worse but no glycosuria was found upon repeated urinalysis. Examination of the blood during the aglycosuric period revealed a blood-sugar concentration ranging from 480 to 633 milligrams per 100 cubic centimeters. The administration of insulin resulted in the reduction of the blood sugar and general subjective and objective improvement. Under ordinary conditions, from a therapeutic standpoint more reliance is to be placed on the quantity of glucose eliminated in the urine than upon the blood-sugar concentration. At times, however, for reasons not at all obvious, sudden alterations occur in renal permeability with no demonstrable evidence of kidney damage, with consequent fluctuation in the mythical but convenient "renal threshold" for glucose. In view of this fact, determinations of blood sugar should constitute an essential part of the routine management of all patients with diabetes, particularly in the event of the development of complications, regardless of the presence or absence of glycosuria. Routine estimations of plasma cholesterol during the period of treatment will likewise prove to be of distinct value.

The occurrence of gangrene of the feet in diabetes is believed to be dependent largely upon a decreased blood supply due to arteriosclerosis which is so common a complication of this disorder. With the possible exception of early diagnosis and adequate treatment of the diabetes, little can be done at the present time to prevent the development of arteriosclerosis, the etiology of which is not known. However, the early recognition of circulatory disturbances in the extremities may, by rendering possible the institution of measures designed to increase local circulation, prevent or postpone the occurrence of gangrene. The skin reaction to histamin, shown by Sir Thomas Lewis to be dependent upon adequate circulation, was utilized by Starr as a means of estimating the condition of the circulation and the resistance of the extremities to infection in 100 cases of diabetes with and without gangrene.

The following technic was employed: "The patients were placed flat on their backs with the legs extended. Areas of normal skin were cleansed with alcohol and after complete evaporation a drop of the histamin solution (1:1000 histamin acid phosphate solution containing 0.5 per cent. of chloretone) was placed on the surface. With a sharp needle the skin was pricked seven times through the drop, the pricks forming a circle about 5 millimeters in diameter, the needle going well into the skin but not deep enough to draw blood. Usually one test was placed above the knee, one about 6 inches below the patella, a third 6 inches above the ankle, a fourth on the dorsum of the foot; in special cases other situations were tested. The resulting reactions were roughly sketched at two and a half, five, ten and fifteen minutes after initiating them. The reactions normally resulting resemble mosquito bites; first a red spot appears, followed and obliterated by a wheal, surrounded by a reddened area (flare) several centimeters in diameter; a sensation of itching accompanies the reaction.

"The normal reaction is complete (that is, both wheal and flare present) within five minutes and the reactions on the foot closely resemble those on the leg and thigh, the distal usually appearing a little slower and being a little less well formed than the proximal. Evidence of diminished circulation in the feet consists of delay in appearance and imperfect development of the reaction on the foot, while the reaction above the knee remains normal."

It was found that 32 per cent. of 100 unselected diabetic patients under treatment had a normal circulation in the feet; in 34 per cent. there was moderate impairment and in 34 per cent. marked impairment of the circulation as evidenced by the response to histamin. In many instances involvement of the smaller arteries may be determined by means of this test when palpation of the larger arteries fails to reveal definite sclerotic changes. The clinical value of this procedure lies in its ease of performance and in the fact that it may lead to the discovery of circulatory changes in diabetics at a time when collateral circulation may be encouraged by either local or general measures. If gangrene has developed the histamin response may aid in selecting the most suitable mode of treatment and in choosing the level at which amputation may be successfully performed.

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ADDISON'S DISEASE

One of the most important contributions to organotherapy in an age characterized by advances in this field is furnished by the apparently successful extraction of a potent extract of the suprarenal cortex by Swingle and Pfiffner.¹ Ever since the original description of the clinical entity known as Addison's disease and the establishment of suprarenal insufficiency as its etiological basis, attempts have been made to apply substitution therapy in the form of epinephrine and the whole suprarenal gland substance. On the basis of clinical observation and experimental investigations on adrenalectomized animals, it became obvious that the cortical rather than the medullary substance (epinephrine) was the most essential factor in this condition and was essential to life. Because of the relative inefficacy of the oral administration of suprarenal cortex, it became necessary that an active extract be prepared which could be administered hypodermically or intravenously. This has apparently been accomplished, and the life of bilaterally adrenalectomized animals may be maintained by means of the extract prepared by Swingle and Pfiffner.²

Rowntree, Greene, Swingle and Pfiffner³ report the results of the use of this preparation in the treatment of seven patients with Addison's disease. These results are so strikingly beneficial in controlling the severe manifestations of the disease that it seems probable that the preparation of an accurately standardized commercial product will be of inestimable value in the management of a condition which until the present time has successfully resisted practically all therapeutic measures. The following plan of treatment is suggested by Rowntree and his associates:

(1) The treatment of dehydration, which occurs during the crises, by the administration of 10 per cent. dextrose and 1 per cent. sodium chlorid solutions.

(2) The institution of the Muirhead treatment, which appears to be effective in a considerable proportion of cases and under which a number of patients have survived for several years. This consists in the administration of epinephrine to the point of tolerance, by mouth, by rectum and subcutaneously, at repeated intervals during the day and in the maximum tolerated dosage. This is supple-

mented by the oral administration of whole suprarenal substance or suprarenal cortex.

(3) The administration of the cortical hormone which is markedly effective during the crises, acting usually within forty-eight to seventy-two hours. In five instances, in the presence of a crisis or impending crisis, 40-60 cubic centimeters of an aqueous solution of the extract in divided doses, over several days, temporarily restored the patients to apparent health. The effects lasted for a period of from one to three weeks.

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LIPOID NEPHROSIS

The subject of lipoid nephrosis occupies a prominent place in the medical literature of the past year. As in previous years there is considerable controversy as to whether the clinical condition designated lipoid nephrosis is a distinct entity or whether it represents a stage in the development of chronic nephritis. Following the original introduction of the term nephrosis by Müller in 1905, Volhard and Fahr in 1914 placed under this designation a group of cases characterized by oliguria, marked albuminuria, extensive edema, lipoidemia and absence of hematuria, hypertension, cardiac hypertrophy and manifestations of renal insufficiency. Histologically the kidneys showed tubular degeneration with lipoid deposits in the cells of the tubules and in the interstitial tissue, the glomeruli being normal. Munk added to this picture the presence of doubly refractive lipoid bodies in the urine. Epstein, in 1917, was the first to emphasize the fact that in this condition the total protein of the blood plasma or serum is markedly diminished, the reduction occurring practically entirely in the albumin fraction with consequent diminution in the ratio of albumin to globulin. He proposed the hypothesis that lipoid nephrosis is of extrarenal origin, being primarily a disorder of protein metabolism accompanied by a subnormal basal metabolic rate. Epstein later suggested that the term "neph-

an hour as much as 60 per cent. may have been removed from the blood-stream and excreted in the urine.

There is little doubt that many cases are designated lipoid nephrosis which are in reality chronic nephritis. However, it appears to have been satisfactorily demonstrated that the condition, although rare, does exist as a clinical entity.

One of the outstanding results of the widespread interest in this condition has been intensive investigation of the significance of the plasma proteins in their relation to water balance and edema. Great advances have been made in our understanding of certain phases of this subject which have important therapeutic applications. In 1928, Leiter demonstrated that edema could be produced in animals by diminishing the concentration of serum proteins. This was done by plasmapheresis, which consists in bleeding the animals, separating the plasma from the cells, replacing the plasma by an equal volume of physiologic salt solution and reinjecting the cell-saline suspension. This procedure was applied by Barker and Kirk to a study of experimental edema in dogs in relation to edema of renal origin in patients. By withdrawing 400-900 cubic centimeters of blood and reinjecting the cells from four to six times a week the serum protein was gradually decreased, the reduction occurring almost entirely in the albumin fraction. At the end of about six weeks the serum protein had fallen to 4-4.5 gm. per 100 cubic centimeters, the albumin being 1 gm. and the globulin 3-3.5 gm. per cent. At this time slight edema was noted. When this stage had been reached edema could be made to develop and to disappear at will by continuing or omitting plasmapheresis.

Peters, Wakeman, Eisenman and Lee had made the observation that edema is usually present when the serum protein falls below 4 gm. per 100 cubic centimeters. Barker and Kirk found that the level of serum albumin is a much more reliable index of the time of appearance and the amount of edema than is the total serum protein. Edema always appeared when serum albumin fell below 0.8 gm. per 100 cubic centimeters and disappeared when it rose above 1 gm. per 100 cubic centimeters. This was apparently independent of the serum globulin.

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the urine. These consisted of albumin, hyalin and granular casts, fat globules, renal epithelium and, occasionally, red and white blood-cells. The specific gravity at first was, consistently high (1.030-1.040), but later fell to 1.010 coincidently with an increase in blood-pressure and a distinct tendency toward diminution of the edema. These phenomena were interpreted as indicative of progressive renal damage. Histologic examination of the kidneys supported this view, the changes varying from slight cloudy swelling of the tubular epithelium with fatty infiltration to extensive tubular degeneration, fibrosis and glomerular damage.

These observations are applied by the authors to the interpretation of the pathological physiology and etiology of nephrosis as it occurs clinically. They state, "In our patients we feel that the early kidney change is predominantly a tubular one, and that the primary lesion was due to acute nephritis or, as in few cases, was obscured. After a variable period of time of albuminuria, the serum depletion occurred, and edema and the rest of the picture typical of nephrosis appeared. These patients usually do not die at this stage unless some severe intercurrent infection, to which they are predisposed, develops. After a variable length of time of such an albuminuria, edema, etc., the blood pressure increases, the heart enlarges, changes in the eye-grounds occur, the results of renal function tests decrease, the blood urea nitrogen increases, the amount of albumin in the urine diminishes, casts and cellular elements increase, edema disappears and the disease picture gradually passes from one of tubular nephritis to one of glomerular changes; finally, the patient dies of uremia. The pathologic change in the kidney is one of a chronic mixed or diffused nephritis with marked tubular, glomerular and interstitial changes."

These conclusions, predicating the existence of an underlying renal lesion in nephrosis, do not appear to be justified on the basis of the experimental data which were presented. Indeed, both the nature of the study and the results obtained lend support to the opposite view that the primary and fundamental error is a disturbance of protein metabolism and that the pathologic changes in the kidney are secondary in nature and are to be considered rather as complicating lesions than as a part of the disease entity. Furthermore, there is evidence that the serum protein concentration may

rosis" should be discarded as misleading and the condition designated by the more descriptive term "diabetes albuminuricus."

Those who disclaim the existence of lipoid nephrosis as a pathological entity believe that it is merely a form of chronic nephritis with extensive degenerative changes in the tubules; early in the course of the disease the glomeruli show little or no change but later lesions appear which progress into typical chronic glomerular nephritis. The renal lesion results in albuminuria, which, if prolonged and excessive, is followed by a reduction in the concentration of albumin in the blood plasma. The elimination of albumin is the result of either injury to the glomerular and capsular epithelium by an acute diffuse nephritis which has subsided (Elwyn) or a functional alteration in the glomerular capillary walls which permits the passage of albumin (Christian).

Those who affirm the clinical and pathological identity of lipoid nephrosis believe that glomerulonephritis, when it occurs in association with that condition, is a result of the excessive strain incident to the continued excretion of large quantities of albumin by the glomeruli. It must be admitted that the burden of proof rests upon the former group of clinicians and pathologists, for undeniably authentic cases of pure lipoid nephrosis have been reported by reliable authorities. Many confusing factors inherent in a study of renal disease in adults do not enter into similar investigations in children. Wolbach and Blackfan reported a clinical and pathological study of eight fatal cases of so-called acute tubular nephritis in children from one to six years of age. All conformed to the clinical picture of nephrosis as described above. The kidneys in each instance exhibited degenerative changes in the epithelium of the convoluted tubules. In four cases there were small cicatrices which were evidently the end-result of complete necrosis of the tubules and consequent elimination of glomeruli. The authors regard the renal lesions as the effects of the disease covering the relatively brief period of illness immediately preceding death, since similar lesions of even greater severity may be produced in a few days in severe infections and toxic conditions such as those present as a terminal event in these cases (hemolytic streptococcus and pneumococcal infections). They conclude that the renal lesions cannot explain the pathologic physiology of the disease and there-

fore do not believe that the primary effect of the etiologic agent is upon the kidneys or that the important manifestations of the disease are consequences of injury specific to those organs. They state further that any name implying a renal origin, such as nephrosis or tubular nephritis, is misleading and inappropriate.

Shapiro likewise believes that pure lipoid nephrosis does exist, being fundamentally a disturbance of lipoid-protein metabolism. The prominent rôle assumed by the kidneys in the clinical and pathologic picture of the disease is due to the secondary involvement of those organs as the excretory pathways for the products of disturbed metabolism. He states that the renal changes are first evidenced by hyperactivity of the renal epithelium, gradually proceeding to exhaustion atrophy and degeneration of the cells of the tubules. As the condition progresses the interstitial tissue proliferates and later shrinks, resulting in constriction of the glomeruli and contraction of the kidneys which are at first smooth but, in the event of tubular regeneration, become granular.

Shapiro insists upon the importance of distinguishing between renal amyloidosis and lipoid nephrosis since amyloid disease of the kidney does not always result in lipoid nephrosis. When they appear together they are separate consequences of a common injury. The importance of this distinction lies in the fact that whereas lipoid nephrosis is a relatively benign condition, amyloidosis, if fully developed, is an irreversible condition with an extremely grave prognosis. It is believed, however, that if recognized early, the process may be corrected. The Congo-red test, used extensively in Europe, is advocated as a means of early diagnosis of this condition and also as a method of differentiating between nephrosis and chronic nephritis with a nephrotic component. This test depends upon the fact that Congo-red, injected into the blood-stream, is excreted slowly by the liver, none of the dye appearing in the urine and about 80 per cent. remaining in the blood-stream at the end of an hour. In amyloidosis, due to the marked specific affinity of amyloid for the dye, it disappears from the blood with such extreme rapidity that 60-100 per cent. may be removed within an hour, none, however, appearing in the urine. In nephrosis, on the other hand, the kidneys are abnormally permeable to Congo-red so that at the end of

an hour as much as 60 per cent. may have been removed from the blood-stream and excreted in the urine.

There is little doubt that many cases are designated lipoid nephrosis which are in reality chronic nephritis. However, it appears to have been satisfactorily demonstrated that the condition, although rare, does exist as a clinical entity.

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Of particular interest was the observation that following the development of edema, evidences of renal damage began to appear in

the urine. These consisted of albumin, hyalin and granular casts, fat globules, renal epithelium and, occasionally, red and white blood cells. The specific gravity at first was, consistently high (1.030-1.040), but later fell to 1.010 coincidently with an increase in blood-pressure and a distinct tendency toward diminution of the edema. These phenomena were interpreted as indicative of progressive renal damage. Histologic examination of the kidneys supported this view, the changes varying from slight cloudy swelling of the tubular epithelium with fatty infiltration to extensive tubular degeneration, fibrosis and glomerular damage.

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One of the outstanding results of the widespread interest in this condition has been intensive investigation of the significance of the plasma proteins in their relation to water balance and edema. Great advances have been made in our understanding of certain phases of this subject which have important therapeutic applications. In 1928, Leiter demonstrated that edema could be produced in animals by diminishing the concentration of serum proteins. This was done by plasmapheresis, which consists in bleeding the animals, separating the plasma from the cells, replacing the plasma by an equal volume of physiologic salt solution and reinjecting the cell-saline suspension. This procedure was applied by Barker and Kirk to a study of experimental edema in dogs in relation to edema of renal origin in patients. By withdrawing 400-900 cubic centimeters of blood and reinjecting the cells from four to six times a week the serum protein was gradually decreased, the reduction occurring almost entirely in the albumin fraction. At the end of about six weeks the serum protein had fallen to 4-4.5 gm. per 100 cubic centimeters, the albumin being 1 gm. and the globulin 3-3.5 gm. per cent. At this time slight edema was noted. When this stage had been reached edema could be made to develop and to disappear at will by continuing or omitting plasmapheresis.

Peters, Wakeman, Eisenman and Lee had made the observation that edema is usually present when the serum protein falls below 4 gm. per 100 cubic centimeters. Barker and Kirk found that the level of serum albumin is a much more reliable index of the time of appearance and the amount of edema than is the total serum protein. Edema always appeared when the serum albumin fell below 0.8 gm. per 100 cubic centimeters and disappeared when it rose above 1 gm. per 100 cubic centimeters, being apparently independent of the serum globulin concentration.

Of particular interest was the observation that following the development of edema, evidences of renal damage began to appear in

the urine. These consisted of albumin, hyalin and granular casts, fat globules, renal epithelium and, occasionally, red and white blood-cells. The specific gravity at first was, consistently high (1.030-1.040), but later fell to 1.010 coincidently with an increase in blood-pressure and a distinct tendency toward diminution of the edema. These phenomena were interpreted as indicative of progressive renal damage. Histologic examination of the kidneys supported this view, the changes varying from slight cloudy swelling of the tubular epithelium with fatty infiltration to extensive tubular degeneration, fibrosis and glomerular damage.

These observations are applied by the authors to the interpretation of the pathological physiology and etiology of nephrosis as it occurs clinically. They state, "In our patients we feel that the early kidney change is predominantly a tubular one, and that the primary lesion was due to acute nephritis or, as in few cases, was obscured. After a variable period of time of albuminuria, the serum depletion occurred, and edema and the rest of the picture typical of nephrosis appeared. These patients usually do not die at this stage unless some severe intercurrent infection, to which they are predisposed, develops. After a variable length of time of such an albuminuria, edema, etc., the blood pressure increases, the heart enlarges, changes in the eye-grounds occur, the results of renal function tests decrease, the blood urea nitrogen increases, the amount of albumin in the urine diminishes, casts and cellular elements increase, edema disappears and the disease picture gradually passes from one of tubular nephritis to one of glomerular changes; finally, the patient dies of uremia. The pathologic change in the kidney is one of a chronic mixed or diffused nephritis with marked tubular, glomerular and interstitial changes."

These conclusions, predicated on the existence of an underlying renal lesion in nephrosis, do not appear to be justified on the basis of the experimental data which were presented. Indeed, both the nature of the study and the results obtained lend support to the opposite view that the primary and fundamental error is a disturbance of protein metabolism and that the pathologic changes in the kidney are secondary in nature and are to be considered rather as complicating lesions than as a part of the disease entity. Furthermore, there is evidence that the serum protein concentration may

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be subnormal in humans for considerable periods of time without the development of organic changes in the kidneys. Bennett, Dodds, and Robertson report six cases with subnormal plasma protein concentrations due to different causes which illustrate the fact that depletion of the plasma proteins from any cause leads to edema. These patients differed from those with lipoid nephrosis in that the cholesterol content of the blood was not increased and albuminuria was not observed. There was no clinical evidence of renal damage in any instance and postmortem examination in three of the cases revealed normal kidneys. In three of these patients the low serum protein was apparently secondary to the presence of ascites, the ascitic fluid having a high protein content. Similarly, Landis and Leopold observed patients with inanition edema, the low serum protein in these cases being due to tuberculous enteritis and restriction of the intake of protein in the diet. The edema in such cases was shown to be dependent directly upon the diminished osmotic pressure of the plasma colloids incident to the decreased protein concentration.

The fact that edema may result from a restricted intake of protein has been recognized for many years in the condition termed inanition edema which was prevalent in prison camps during the World War. Recently, Frisch, Mendel and Peters demonstrated that edema can be produced in experimental animals by the prolonged administration of diets containing very small amounts of protein. However, it is only within recent years that the profession has been weaned from the belief that urinary evidence of renal damage, particularly albuminuria, is an indication for protein restriction. It is in this connection that the results of studies of nephrosis have an important therapeutic application.

Epstein several years ago emphasized the value of high protein diets in the treatment of lipoid nephrosis, a fact which has since been repeatedly substantiated. The relationship between edema, serum proteins and protein intake has been beautifully demonstrated by Cowie, Jarvis and Cooperstock in a metabolic study of a child, six years of age, suffering with chronic glomerulonephritis and nephrosis. It was found that edema and ascites could be induced and made to disappear by decreasing or increasing the protein intake, just as Barker and Kirk were able to do by varying the

serum protein content by plasmapheresis. Nitrogen balance studies were performed during alternate edema and edema-free periods. A point of particular interest was the observation that the output of albumin in the urine remained practically unchanged during periods of adequate and inadequate protein feeding; however, when the protein intake was greatly increased the albumin output was likewise increased about 150 per cent, although the edema had disappeared.

When sufficient protein was given to bring the patient into a positive nitrogen balance of from 1 to 3.7 gm. edema disappeared, and if a continuous positive balance of from 2 to 5 gm. was maintained the edema did not recur. A protein intake of 2.6 gm. per kilogram of body weight was required to secure these positive nitrogen balances, an amount far in excess of that necessary for a positive nitrogen balance in healthy children of the same age. The fact that there was no increase in the nitrogen content of the blood or other body fluids associated with this increased intake indicates that a large amount of the ingested protein was stored in the tissues. The serum proteins were low during the periods of edema and low protein intake and were also subnormal, although tending to increase, during the periods of high protein feeding and absence of edema. The blood cholesterol was high (525-704 mg. per 100 cubic centimeters), and the serum globulin fraction always exceeded the albumin, the albumin-globulin ratio varying from 0.24 to 0.80, averaging 0.54.

This study illustrates the relation of protein metabolism to edema, particularly in nephrosis, but also, apparently, in nephritis. The serum protein level is not the only factor of importance, as evidenced by the observation that edema may be absent in the presence of a low serum protein level (3.8 gm. per 100 cubic centimeters) if a positive nitrogen balance is maintained. The therapeutic significance of these findings is obvious. In nephrosis and in chronic nephritis with edema without nitrogen retention and with hypoproteinemia, protein, far from being restricted, should be given in amounts in excess of those required by normal individuals. Whereas excessive protein feeding, by increasing the amount of albumin eliminated in the urine, may eventually result in increased renal damage, a protein intake adequate for the establishment of a positive nitrogen balance and the relief of edema may be

be subnormal in humans for considerable periods of time without the development of organic changes in the kidneys. Bennett, Dodds, and Robertson report six cases with subnormal plasma protein concentrations due to different causes which illustrate the fact that depletion of the plasma proteins from any cause leads to edema. These patients differed from those with lipoid nephrosis in that the cholesterol content of the blood was not increased and albuminuria was not observed. There was no clinical evidence of renal damage in any instance and postmortem examination in three of the cases revealed normal kidneys. In three of these patients the low serum protein was apparently secondary to the presence of ascites, the ascitic fluid having a high protein content. Similarly, Landis and Leopold observed patients with inanition edema, the low serum protein in these cases being due to tuberculous enteritis and restriction of the intake of protein in the diet. The edema in such cases was shown to be dependent directly upon the diminished osmotic pressure of the plasma colloids incident to the decreased protein concentration.

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tained without increasing the albumin output. The realization is gradually growing that patients not only with nephrosis but also with nephritis must be considered from a broader viewpoint than has hitherto been deemed necessary.

INTRAVENOUS UROGRAPHY

The usefulness of the Roentgen-ray as a diagnostic aid has recently been greatly enhanced by the development of a radio-opaque halogen compound which is excreted almost entirely by the kidneys. Prior to 1928 Binz and Räth had succeeded in synthesizing an iodine-containing compound known as Selectan Neutral which, being largely excreted in the urine, enable them to visualize the urinary bladder by means of the Roentgen-ray. Unless ureteral obstruction was present or was secured by ligation or occlusion by the introduction of a bougie from below, the pelvis and ureter could not be clearly outlined. Furthermore, following the administration of effective amounts of the substance, toxic manifestations occurred quite frequently. These difficulties were soon surmounted by the aid of synthetic chemical procedures which have contributed so largely to the advancement of modern medicine.

Roseno succeeded in producing a compound containing urea and iodine which he called pyelognost and which permitted better visualization of the upper urinary passages than could be obtained with the use of Selectan Neutral. The most satisfactory substance thus far produced was developed by Swick and Lichtenberg and termed, by them, Uroselectan. It is a modification of the original preparation of Binz (5-iodo-2-pyridon-N-acetate of sodium). It is neutral in reaction, more than 50 per cent. soluble in water, contains 42.2 per cent. of iodine, is extremely stable and apparently non-toxic in doses far in excess of those ordinarily employed. It is excreted as such by the renal glomeruli, about 90 per cent. being recovered from the urine within eight hours following its injection intravenously. It is practically entirely removed from the bloodstream in four hours. Since the density of the shadow and the consequent degree of visualization of the upper urinary tract depends upon the rate of excretion and the ability of the kidney to concentrate the iodine compound, the success of this method of urography is dependent to a considerable extent upon the integrity

of renal glomerular functional activity. In the presence of normal renal function the entire urinary tract is usually clearly outlined in fifteen minutes after the administration of Uroselectan.

Since the introduction of this method of urologic study into this country by Swick, it has been used extensively with eminently successful results. Uroselectan is administered in the following manner:

A 40 per cent. solution in doubly distilled water is filtered and sterilized by autoclaving for twenty minutes. The resulting brown solution is brought to body heat in a water bath and injected slowly intravenously, preferably in two equal doses at an interval of two to three minutes, by either the syringe or the gravity method. The dosage recommended is as follows:

Infants and young children—20 cubic centimeters of the 40 per cent. solution; 5-10 years—40 cubic centimeters of the 40 per cent. solution; 10-15 years—60 cubic centimeters of the 40 per cent. solution; Adults—100 cubic centimeters of the 40 per cent. solution.

After the ordinary preparation a preliminary exposure is made prior to the injection and then a quarter of an hour, three quarters, and one and a quarter hours, after injection. In certain cases in which rapid elimination of the compound occurs the exposures must be made at more frequent intervals in order to obtain the best possible visualization.

Lichtenberg has proposed the following indications for intravenous urography:

(1) Whenever, for anatomical, pathological or technical reasons it is impossible or impracticable to employ cystoscopy, ureteral catheterization or pyelography.

(2) In ureteral obstruction.

(3) Whenever instrumental pyelography carries with it an element of risk for the patient.

It is obviously, therefore, of great value in children, in cases of transplantation of the ureters, in hematuria and in cases in which ureteral obstruction prevents the passage of the ureteral catheter and the opaque material into the pelvis from below. It also eliminates the hazard incident to simultaneous bilateral pyelography by the retrograde method and enables the ready comparison of the intensified renal shadows and urinary passages.

Certain contra-indications must be kept in mind. The most

important and perhaps the only serious contra-indication is the presence of uremia or an advanced degree of impairment of renal function, particularly in acute and chronic glomerulonephritis. Other possible but not absolute contra-indications are thyrotoxicosis, pregnancy, active tuberculosis, and advanced circulatory disease.

Intravenous urography cannot, evidently, replace cystoscopy and ureteral catheterization in the advantage to be obtained by the latter procedure in direct visualization of the bladder mucosa and ureteral orifices. It constitutes, nevertheless, a distinct advance in our readily available methods of diagnosis of disorders of the upper urinary tract.

THE —SH GROUP IN CANCER AND TREATMENT OF ULCERS

The solution of a purely biological problem, namely, the essential chemical difference between resting cells and those undergoing mitosis, has resulted in a definite advance in the treatment of ulcers. F. S. Hammett¹ found that sulphur in the form of the —SH or sulphydryl group is present in dividing cells in both animal and vegetable kingdoms,² and is an essential substance in the regeneration of tissues and in the production of benign neoplasms such as papillomas.³ As the growing cells approach maturity the oxidate products and other derivatives of the —SH group following the law of mass action become more and more inhibitory to growth until a state of equilibrium is reached.

Search for compounds containing the —SH group was rewarded in the finding of p-thiocresol, which, when applied to the ears of rats over a space of six weeks, produced a very marked hypertrophy without any attendant inflammatory changes. It was then used on refractory ulcers and bed sores in a solution of 1-10,000 (Reimann^{4, 5}) and applied for periods of forty-eight hours. P-thiocresol was found in all cases treated to stimulate mitosis, to inhibit bacterial growth because of the presence of the cresol radical and thus produce rapid healing.

Interest is now focused on further experimentation on the derivatives of the —SH group in their relationship to growth in malignant neoplasms.

Numerous objective approaches to the treatment of wounds and ulcers have been made. Believing that a lowered metabolism is

detrimental in certain cases to healing, Lauber,⁶ of Kiel, attempted to increase metabolism by the administration of thyroid preparations. He reports favorable results. Lévai⁷ demonstrated in numerous cases at the Poliklinik in Budapest the efficacy of five units of insulin applied on gauze lightly covering a wound. Still another method of accelerating wound healing is reported by Fukase of Vienna⁸ who finds that Roentgen-ray exposure of a long incision in the skin of a rabbit tends to produce healing by first intention, whereas a similar incision not so treated heals by second intention.

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OBSTETRICS AND PEDIATRICS

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PUERPERAL FEVER

Bacteriology.—"Does the vaginal bacterial flora produce puerperal fever?" is the disputed question upon which investigators continue to express antipodal opinions. Shall it still be said with Doederlein that vaginal bacteria in the normal pregnant woman are harmless, or with Brumm that "the danger arises from without," or must the dictum now be changed to, "the danger arises from within"?

The point is made by Colebrook,¹ working at Queen Charlotte's Hospital in London, that precise bacterial diagnosis in puerperal fever is seldom made. In the average case the blood culture is negative and the cervical culture grown under aërobic conditions shows a heterogeneous growth. If hemolytic streptococcal colonies are present, it is assumed—certainly not always rightly—that this organism was the causative one. In the absence of hemolytic streptococci the cause of the infection is listed as "undetermined," unless recourse is made to laborious examination of the blood for antibody response. Anaërobic cultures must be made if there is to be any accuracy in the determination of the etiological organism.

Taylor and Wright,² in their bacteriological study of vaginal flora of 1,100 women immediately before delivery and of 250 of these on the third day of puerperium, came to the conclusion that the bacteria of most importance are those entering the genital tract during or after labor. The non-hemolytic streptococcus and staphylococcus albus were often found before delivery. The relatively innocuous hemolytic streptococcus found before delivery may, in the course of the delivery, enter the uterus and be cultured from the lochia and not produce infection. The maximum growth of streptococci in the uterine cavity occurs, according to Armstrong, and Burt-White³ on the third to fifth day after delivery. Shortly

after it diminishes. Hemolytic streptococci gaining admission during labor have the most devastating effect—Brown⁴ feels that puerperal infections due to ordinary pathogenic organisms are, in most instances, introduced infections. When puerperal fever appears during the second week of puerperium it is usually due, according to Davis,⁵ to chronic gonorrhea.

To oppose some of these ideas comes Schottmüller,⁶ who, in the study of twenty-eight cases of puerperal fever, vigorously asserts that every woman harbors pathogenic organisms capable of causing a fatal child-bed fever. Very significant in this regard is the experimental evidence of Miller and Whitaker⁷ that the bactericidal power of the blood, after rising steadily during pregnancy, undergoes a rapid fall at the time of labor. Schottmüller reports prevalence of the colon and gas bacillus. The hemolytic streptococcus was seldom found, but the anaërobic streptococcus and staphylococcus were found in the majority of cases. This adds strength to Brown's statement⁴ that infections due to the anaërobic streptococcus are usually endogenous.

That anaërobic streptococci are the blood invaders to be reckoned with in puerperal fever is shown by Colebrook,¹ who in seventy-six cases isolated anaërobic bacteria in pure or mixed culture from the blood of eighteen of them.

In the December number of *INTERNATIONAL CLINICS*, Tritsch and Shields⁸ of The Fifth Avenue Hospital in New York have listed the incidence of postpartum fever in various obstetrical maneuvers, thereby showing the relationship between postpartum fever and trauma. The percentage of those developing such fever was in 535 forceps cases, 9 per cent.; in Caesarian section, 31 per cent.; in version, 21 per cent.; in uterine packing cases, 23 per cent.; in breech extraction, 4 per cent. Significant is the finding that use of the low forceps was attended by incidence in 6.7 per cent. of cases of postpartum infection—the same average as that in the entire series of 1,694 cases, including spontaneous labors.

Therapeutic Measures.—Schottmüller⁶ lines up all the used remedies and discards most of them. He advises bimanual examination to determine the site of infection; whether it be in the endometrium of an infected gravida in which case it is harmless; whether it has as its seat the lymphatic system in the parametrium

which carries with it a 50 per cent. mortality; whether it is an endophlebitis or thrombophlebitis, 90 per cent. fatal. Attempts to sterilize the uterus with collargol, rivanol, *etc.*, administration of antipyretics and alcohol, injection of specific and non-specific vaccines and proteins, such as aolan, are all useless measures. Ligation of veins proximal to involvement is indicated at times: The more radical procedure of ligation of the vena cava is discouraged. On the other hand, Fels and Bettinger,⁹ working at the Frauenklinik in Breslau, feel that good results may be obtained ligating the aorta if proper ligature material (strip of fascia lata) is used. Hysterectomy (Schottmüller⁶) is done only in cases of gas bacillus infection. Indispensable to the treatment is intravenous and rectal administration of glucose and fluid. Adrenalin given with glucose intravenously by the continuous drop method (2,500 cubic centimetres of 2 per cent. glucose) over a period of several days may help. Intravenous strophanthin, too, is of some benefit.

Emphasis is placed upon the value in massive transfusion. When the fever is caused by the hemolytic streptococcus, 50 to 100 cubic centimeters of scarlet fever serum is beneficial. Moore¹⁰ gives antistreptococcal serum in doses of 50 cubic centimeters and follows it by 3 to 10 grains of quinine every three hours. Küstner¹¹ gives the serum in a dose of 100 cubic centimeters. Back in 1923, Luker¹² found that intramuscular injections of acid quinine hydrochlorid combined with antistreptococcal serum was very effective. Speaking of quinine—Mitchell¹³ recommends its use for one week following delivery. He draws a rather black picture of what is taking place immediately after delivery. Surely with poor uterine contractions, with a blood clot in the uterus in which organisms may thrive, with the presence of streptococci increasing in the uterus in the first few days after delivery (Armstrong and Burt-White³) and with sudden fall of bactericidal power of the blood (Miller and Whitaker⁷) the stage is completely set for puerperal septicemia. Quinine is said to prevent uterine relaxation at this critical time.

Nahmmacher¹⁴ extols the use, in endometrial infections, of old-fashioned sticks of granulated charcoal which, through its adsorptive power, inhibits the growth of bacteria. Working at the Hessische Hebammenlehranstalt in Mainz he has found remarkable benefits through its use as a prophylactic agent when applied to the inside

of a uterus opened by Caesarian section after rupture of the membranes. He used it routinely in cases of infected abortion either before or after evacuation. The third indication for its use, he points out, is in cases of puerperal endometritis. Nahmmacher's routine in treating these cases is as follows: When the evil-smelling discharge appears, the patient's head is raised 25 centimeters. To further facilitate drainage, ergotin or gravitol, 40 drops of either on three successive days, is given. Should there be no amelioration of symptoms in six days, charcoal sticks are introduced into the uterine cavity. Invariably, in from twenty-four to forty-eight hours following the introduction of charcoal in his series of cases, the temperature fell to normal and the fetid odor disappeared.

Delivery of Occipito-posterior Presentations.—When to allow a posterior occiput presentation to deliver spontaneously, when to treat such a case by elective version, when to apply forceps, is ably discussed by Vaux¹⁵ in his statistical summary of a study of 212 cases of posterior occiput positions occurring over a period of thirty months at the Philadelphia Lying-In. During this time there were in all 1,268 deliveries on his service.

Interference of posterior positions is not justified until the cervix is fully dilated and effaced and until the fetal head is at or near the mid-pelvis. Fetal and maternal mortality rise when the head is allowed to become impacted in an effort to allow nature to take its course. That "watchful waiting" is the best obstetrician does not apply in the presence of a dilated cervix, ruptured or unruptured membranes and no sign of downward advance or rotation of the posterior occiput.

The utter importance of the all too often neglected early vaginal examination to determine the position one has to deal with, comes to light in those border-line cases of moderately contracted pelvis where recourse to Caesarian section is a serious consideration. In such cases surgical induction by means of bougie and rectal tube was done in 1.8 per cent. of times, usually two weeks before term. In 74 per cent. of cases the pelvic measurements showed an external conjugate less than 20 centimeters and an internal conjugate below 10 centimeters. Spontaneous delivery occurred in 58 per cent. of cases; in most of the remaining 42 per cent. either version or forceps delivery was done. The double application of forceps (Tucker-

McLain and Piper axis traction forceps) was used in those cases (23.9 per cent.) in which the first stage of labor had been completed for over two hours, and in which the occiput failed to rotate posteriorly.

The Scanzoni maneuver was done in all the cases only after the head had been drawn down and rested on the pelvic floor. Lacerations of the perineum occurred in 28.8 per cent. of forceps cases—a marked contrast with the version cases in which there were 16.6 per cent. lacerations.

As emphasized by Piper in the discussion of the presentation, Vaux does not advocate routine version in these posterior positions. Version is done only where particularly indicated—usually in those cases in which there has been a definite decision to do an elective termination of labor. Elective version was not attempted when the membranes had ruptured before onset of labor. Great care to preserve intact the amniotic fluid resulted in only 5 per cent. of early rupture over against Foulkrod's 50 per cent. With membranes unruptured, version was done in 14.1 per cent. of the 212 cases. Vaux prefers version with the application of aftercoming head forceps to the rotation of the head in mid-pelvis and forceps delivery, even though he did not use it as often in the quoted cases. He is opposed to any maneuver in the small diameter of the pelvis. In the employment of version there were no severe postpartum hemorrhages and no premature separation of the placenta. The fetal mortality was less in elective version. Perineal lacerations were very much the same in the two types of delivery—about 20 per cent. had second-degree lacerations.

Watson, in commenting upon the somewhat radical ideas of Vaux, quotes Hamilton of Edinburgh, who advises change of position from occipito-posterior to occipito-anterior as a prophylactic measure two weeks before the patient is due. He advises placing a folded towel between the anterior superior spine of the mother and the anterior shoulder of the child and holding it there with a binder. In the majority of cases, after twenty-four hours of such treatment, the head becomes engaged in an occipito-anterior position.

Hochne's Sign.—Like a star that appears but once a year to remind us of its existence, is Hochne's sign. Lazarevic,¹⁶ in Yugoslavia, reports a case of a woman twenty-five years old who had a

difficult labor because of abnormal position of the foetus. An injection of a hypophyseal preparation failed to stimulate uterine contractions. Repeated injections of hypophyseal preparations with maintenance of complete uterine inertia (Hochne's sign) was taken as an indication of rupture of the uterus despite entire absence of other signs or symptoms. Laparotomy was done on the basis of the sign; a 12-centimeter tear was found in the uterus while half the foetus and the entire placenta were in the peritoneal cavity.

Aschheim-Zondek Test for Pregnancy.—With the widespread acceptance of the Aschheim-Zondek test as a dependable means of offering the verdict in a woman of pregnant or not pregnant, attention now turns to account for the small 2 or 3 per cent. of human error and to make in the technic of the test such refinements as the use of fewer mice and the diminution of the 100 hours now required to complete the test. Perhaps more complimentary to the men responsible for this discovery than any amount of editorial commentary is the recent "Umfrage" by professors in Germany—Würzburg, Berlin, Düsseldorf, Freiburg, Göttingen, Greifswald—in which there was scarcely a discordant note in praise of the scientific accuracy of the test. Professor Wagner states that even in the very first stages of gestation it is 99 per cent. accurate. It diagnoses the various pathological entities, such as ectopic pregnancy, hydatid mole and chorionepithelioma. In all of Professor Schmidt's 171 cases there were no false reports. Professor Hellmuth¹⁷ has similar results in 25 very questionable cases. The last report of Aschheim and Zondek is that in 700 tests there were 21 failures.

It was through a rather striking piece of deductive reasoning followed by experimentation that the relationship between the anterior pituitary gland and ovulation was brought to light. The curiosity of Aschheim and Zondek was aroused by the fact that the estrus-producing hormone, isolated from the follicular fluid of the ovary by Allen and Doisy when injected into mice, produced marked uterine, tubal and vaginal, but no ovarian, alteration. There must be some other substance, they argued, which initiates the normal cyclic activity of the ovaries—a substance quite independent of this so called "female sex hormone" found in the follicular fluid, the corpus luteum and placenta. They were quite right—this other

substance proved to be a hormone contained in the anterior lobe of the pituitary gland. It was found that in addition to its power to initiate follicular activity and to start the complete ovulation cycle that it also governs the output of the estrus-producing hormone, thereby acting as a sort of superimposed general sex gland. Further new facts in regard to hormones in the pituitary gland have recently been reported by Zondek. He isolated two hormones acting on the ovaries; one, known as Prolan A, bringing on maturation of the follicles, and the other, known as Prolan B, producing luteinization of the follicular granulosa cells.

Frank believes that this hormone, which is widely distributed throughout the animal and vegetable kingdom and in various body tissues and fluids, is responsible for the normal manifestation of all sex phenomena, including the estrual cycle in lower animals and the menstrual cycle. Other authorities differ with Frank, viewing certain sex phenomena as due to the activity of more than one substance, each of which acts in a specific manner. The subject is further complicated by the variety of terms applied to these hormones by different investigators.

A recent article by Allen and Corner, who have contributed largely to the literature of this subject, appears to clarify the situation somewhat. The agents which have been shown to exert important and specific effects upon the sexual cycle may be classified in the following manner:

(1) The anterior pituitary hormone, which influences the ovary in such a way as to cause the ripening of immature Graafian follicles, and the formation of the corpora lutea. This substance is, so to speak the motor of the female sexual apparatus, imitating and setting into activity the sexual cycle. It acts only in the presence of the intact ovary.

(2) The ovarioplacental hormone which is present in the Graafian follicle, the placenta, the amniotic fluid, the blood and urine, being found in increased concentration in the blood and urine during pregnancy. This hormone (follicular hormone) essentially prepares the uterus for menstruation. This action is effected in castrates as well as in the presence of the immature or mature ovary. Some authorities believe that in addition to this agent, a substance is simultaneously elaborated by the corpus luteum which exerts an

inhibitory effect, supplementing the action of the follicular hormone in preparing the endometrium for the reception of the fertilized ovum. In this way the rhythm of the cycle is regulated and the sensitization of the uterine mucosa effected. Retrogression of the corpus luteum, with consequent diminution in the inhibitory action of its hormone, is followed by the phenomenon of menstruation.

(3) This functional cycle is completed by the hypothesis advanced by other investigators of the existence of a hormone which inhibits the activity of that elaborated by the anterior pituitary body, thus suppressing the further ripening of other immature follicles until the cycle in progress has been terminated.

Collip has complicated the picture by the demonstration of the existence of three distinct, chemically differentiated placental hormones. These are alike in that they are capable of producing the phenomenon of estrus in immature female rats. They differ functionally, however, in the following respects:

(1) The first fraction is apparently the ovarioplacental hormone described above.

(2) The second fraction, similar to the first in its action in immature rats, is, however, ineffective in castrates and perhaps acts by stimulating the intact ovary.

(3) The third fraction, in addition to its estrus-producing effect, also coincidentally produces corpora lutea in immature female rats, and causes an increase in the growth of the accessory sex glands of the immature male. It must, therefore, be considered as possessing luteinizing as well as estrogenic properties.

Up to the present time the only practical use to which this understanding of sex hormone activity can be put is in the early diagnosis of pregnancy, uterine or extrauterine. It is certain, however, that in the course of time potent extracts will be available for use in the treatment of the several common manifestations of functional derangements of the female sexual cycle. The various products now on the market have little practical usefulness chiefly because of the difficulty of standardization and the instability of the hormone.

Frank found the ovarian hormone, while Aschheim and Zondek found the anterior pituitary body hormone, in the urine of pregnant women. Each devised a biological test for its recognition. In comparing the time of appearance in the urine of these two hormones—a

matter of importance—it was found that the ovarian hormone seldom appears in the urine before the seventh or eighth week. Only after the twelfth week of pregnancy is it present in large quantities. The pituitary hormone, on the other hand, is present in the urine in large amounts a few days after implantation of the fertilized ovum and reaches its peak as early as one to two weeks after non-appearance of the expected menstruation. This latter remains positive for about five days postpartum (Liese and Auer¹⁹). Furthermore, the ovarian hormone may be found in the urine of non-pregnant women, particularly in those suffering with amenorrheic conditions. The pituitary hormone is stated to be present in the urine only in women who have conceived.

These two hormones were injected into mice; the ovarian hormone produced active desquamation of the vaginal epithelium characteristic of estrus while the pituitary hormone produced two characteristic morphologic reactions in the ovaries: (1) formation of minute intrafollicular hemorrhages, and (2) development of lutein cells. The technic of the Aschheim-Zondek test^{20, 21} need not be gone into for it is well known. Suffice it to say that six infantile mice weighing about 5 or 6 gm. are needed. The mice receive six injections of urine in two days, three on the first day ranging from 0.2 cubic centimeter to 0.3 cubic centimeter, and three on the second day ranging from 0.3 cubic centimeter to 0.4 cubic centimeter. After 100 hours the mice are killed and the ovaries examined. Positive results are shown by increase in size of the ovaries by two or three times and by the appearance on their surface of submiliary yellow protrusions and diffuse red spots. Perhaps the 27 per cent. error in the Aschheim-Zondek test reported by Mazer and Hoffman²² of Philadelphia, who reported results on 314 cases, was due, as they themselves suggest, to the use of only two or three mice instead of the prescribed six. It may be well to mention at this point that they found positive reactions in sixteen of 164 non-pregnant women: In five of these there was menopause; in seven, ovarian hypofunction; in one, ovarian cysts; in one, uterine fibroids; in one, salpingitis with irregular bleeding; and in the last one, amenorrhea. They offer as another possible explanation for the positive findings in non-pregnant women the compensatory pituitary hyperfunction which hypothetically accompanies ovarian deficiency.

Brouha²³ encountered difficulties in the test to the extent of 40 per cent. error. His modification of the test by the employment of male instead of female mice awaits the test of time. Ehrhardt,²⁴ who incidentally reports only 2 per cent. failures in 400 cases, attempted by various means to shorten the 100 hours necessary for the completion of the test. He used to this end splenectomized animals, he used larger quantities of urine, he tested the effect of high temperatures, he performed hysterectomies and unilateral oophorectomies—all to no avail.

Puzzling to the obstetrician and gynecologist are those conditions so closely simulating pregnancy. Even tuberculosis, primary and secondary anemias, psychoses, and metabolic disorders mimic the gravid state. Solms and Klopstock,²⁵ who employed the test in 349 cases, report 99 per cent. accuracy. The test is not only of diagnostic value but also of therapeutic value. In four cases with amenorrheal or menopausal symptoms, the changes in the test animals revealed hypo- or hyperfunction of the sex glands. The hypo-function cases were supplied with the missing hormones. Kaplan²⁶ stresses the value of the test in early diagnosis of pregnancy, even as early as the seventh day after the non-appearance of the menstrual period. The diagnosis of ectopic pregnancy proved to be correct by operative confirmation in three cases of Liese and Auer¹⁹ and in nine cases of Mazer and Hoffman.²² In ectopic gestation and in abortion the test is positive as long as fetal tissue is in biologic contact with the maternal blood. The former investigators stress the value of the test in obese amenorrheic patients and in making the differential diagnosis between fibroids and pregnancy. In cases with hydatid mole and chorionepithelioma a very strong reaction is obtained (Aschheim²⁰). In one such case there was a reaction twelve times stronger than the reaction usually obtained in the second month of gestation. The test should always be made after the expulsion of a hydatid mole. The test may remain positive as long as two months after the expulsion of the mole without any evidence of chorionepithelioma.

Anesthesia in Obstetrics.—New methods are slowly evolving to change the devastating pains of childbirth to tranquil sleep. In the morphine-scopolamin narcosis (twilight sleep) of years ago obstetrical anesthesia went "backward in order to leap the better."

Now it is coming forward with the introduction of new anesthetics and increased knowledge of longer tried procedures.

At the onset of labor, non-depressant barbital preparations, such as ipral and sodium amyta, are being resorted to more and more. Using sodium amyta in over 100 cases, Robbins, *et al.*²⁷ reports that the drug seldom delays the progress of labor. It diminishes the fetal heart rate about 20 beats a minute and has not been proved to cause asphyxia, although Kobes,²⁸ in commenting upon the apathy and peculiar ashen gray color of the infant associated with its use, brings to light the fact that barbituric acid and bromine found in the infant's urine and blood are not fully eliminated until the fourth day after birth. The women, strangely enough, failed to remember that they had cried out with pain during the second stage and that they had been very restless. There was no undue postpartum bleeding, pain, headache or nausea after an intravenous dose of from 1/20 to 1/9 grain per kilogram. The maximum analgesic effect was attained fifteen minutes after the intravenous injection and began to wane after an hour. It is best given after the administration of morphia 1/6 grain and scopolamin hydrobromid 1/150 grain, when the cervix is two fingers dilated and partly effaced and pains occurring at ten-minute intervals. "Nembutal" has just been advocated (1931) by Magill^{27a} as the most valuable of the barbituratic basal hypnotics. It is about twice as toxic as sodium amyta and its action is much shorter. Besides, it causes restlessness and delirium less often. It has been given intravenously, by mouth and by rectum to 262 surgical patients. There is no doubt that nembutal will soon be tried in the obstetrical patient.

During the second stage, nitrous oxide and oxygen to lessen each pain and dependable old-fashioned ether for actual delivery are still considered excellent measures (Editorial²⁹). The former has no effect upon contractions while the latter acts similarly to chloroform in that it diminishes the force of the contractions. Ether plus morphine, however, tends to produce asphyxia in the baby (Wilson^{29a}). Morphine lessens frequency of uterine contractions whereas chloroform is overshadowed by ensuing toxicity. The latter's sudden relaxing influence on Bandl's contraction ring and its tendency to diminish force and frequency of contractions should contra-indicate its use (Furlong³⁰) despite the fact that this effect passes off as soon

as the chloroform, or ether for that matter, is stopped. Connell,³¹ on the other hand—and many will back him—recommends whiffs of chloroform when the head is stretching the perineum.

Gwathmey³² again reports favorably upon the effects of routine rectal anesthesia. That used by him at the present time is composed of 20 grains of quinine alkaloid dissolved in 40 minims of 95 per cent. alcohol, 2½ ounces of ether and 4 ounces of olive oil.

When the cervix is 2½ to 3 fingers dilated with corresponding effacement, and the pains coming every five minutes, and the head engaged, a hypodermic injection of 1/6 to ¼ grain of morphia and an intramuscular injection of 2 cubic centimeters of 50 per cent. magnesium sulphate are given. The magnesium sulphate is repeated twice before delivery. About a half hour after the injection of morphia the Gwathmey anesthetic is given slowly by rectum.

This synergistic anesthesia is most effectively used in primiparae. It is said not to delay the rotation of occipito-posterior heads. It tends to decrease maternal morbidity. Furlong³³ feels that Gwathmey anesthesia should not be used routinely, but only in selected cases, because of the occurrence of such unfortunate accidents as narcosis of the foetus, pulmonary irritation, diarrhea and quinine reaction.

Quinine has come into rather sudden prominence as a reputed analgesic when given during labor. Hill,³⁴ while inducing a labor with quinine-pituitrin, was struck by the almost complete absence of pain. His presumption that quinine was the responsible agent was borne out by experimentation. As a result, he recommends the use of 5 grains of quinine bihydrochlorid given every one to four hours from the suspected beginning of labor. At the time of the first actual pain 1 cubic centimeter of ovarian residue is injected and repeated during the second stage if necessary. In over 400 cases including breech and occipito-posterior presentations in which quinine was used, Mitchell¹³ failed to find a single contra-indication to its use. At the high tide of his enthusiasm he states that the use of small doses of quinine for three weeks prior to the expected date of labor improves the general health of the patient, makes labor easier and shorter, produces uniformly good uterine contractions and does not increase the tendency to premature labor, to precipitate labor, to perineal lacerations or after pains. He uses

R: Quin. sulph.	1½ grains
ac. nitrohydrochlor. dil.	3 mins.
syr. aurant.	½ dr.
aq. ad.	2 dr.
Mitte	8 oz.

Sig. 2 dr. ex aq. i.d. s.a.c.

A note of warning against the promiscuous use of quinine in the induction of labor is sounded by McSwiney,³⁴ who reports two fetal deaths rather obviously due to the use of the usual three 10-grain doses of quinine at two-hourly intervals.

Connell³⁵ at the Dudley Road Hospital, Birmingham, and Reed³⁶ at the Wesley Maternity, Chicago, have published their results with avertin or tribromethylalcohol in the introduction of rectal anesthesia in the second stage of labor. Together they report sixty cases. Connell used 0.075 cubic centimeter of the drug, Reed, 0.055 cubic centimeter per kilogram of body weight. They find that effects show themselves in fifteen minutes and last two hours. Avertin does not produce an entirely painless labor but it does prevent exhaustion, prolonged backache and the "memory of a terrible experience to jaundice her outlook on life." The changes in pulse rate and blood-pressure are insignificant although in a few instances the pains were markedly slowed. The second stage was, as a rule, prolonged by perhaps one-fifth. No laxity of the myometrium, as occurs in chloroform anesthesia, was experienced. After the third stage, which was entirely unaffected, pituitary extract was unnecessary. Parsons³⁷ feels that avertin has been tried and found wanting in England. Indication for its use is limited to a narrow range. It has no appreciable effect upon the cardiovascular system with exception of coronary vessel dilation and blood-pressure lowering. Contraindications to its use are: inflammatory conditions of the colon, renal (81 per cent. of avertin escapes through the kidneys) and hepatic lesions, acidosis, advanced cachexia and blood deficiencies. Edwards³⁸ suggests washing out the patient's rectum upon return from the operating room. The drug requires utmost care in preparation. Postoperative observation is doubly necessary because of the tendency toward relaxation of the jaw and tongue. There have been very favorable accounts of the use of avertin in delivery of hyper-

thyroid cases (Pribram³⁹). In primiparae, whose pains are longest and most severe, does avertin find one of its chief indications (Connell³¹).

Numerous deaths have been attributed directly to the use of avertin, that of König⁴⁰ being the fifty-second. In that case, necropsy revealed in the liver the central lobule atrophy and the fatty infiltration of acute yellow atrophy. It brought a word of caution from him—do not give avertin without first performing a liver function test.

Spinal anesthesia, thus far, has failed to be of much value. Mahon⁴¹ found that it retards markedly the progress of labor and diminishes the rhythmic uterine contractions so much so that the uterus fails to respond to injections of pituitary extract. Delivery could be accomplished only by manual dilatation of the atonic cervix followed by the application of forceps. Stovaine intraspinally does not inhibit contractions, according to Bourne and Burn,⁴² but it does interfere with full relaxation between pains. During the first stage it tends to retard dilatation of the cervix.

The Care of Breasts.—The daily employment of routine measures requiring years of trial before their adoption is one of the truest expressions of progress. The care of breasts, finally arrived at after many years of trial on the Vaux⁴³ and Piper Services at the Philadelphia Lying-In, is outlined below.

Antenatal care begins two weeks before delivery with a daily warm water cleansing of the breasts followed by the application of small amounts of cocoa butter or witch hazel cold cream; this tends to soften the breasts and make them pliable. Instruction is given to avoid restricting the breasts by clothing.

Essential to the healthy breast is its regular use by the baby; not only is it essential to the breast but also to the uterus, whose involution it influences. In preparation of the breasts for the first meal eight hours after delivery, the cloth binder snugly applied is unpinned to expose the breasts. A sterile towel is applied over one breast while the other is being prepared: 1, Sponge areola with tincture of green soap; 2, sponge with sterile water; 3, sponge with 72 per cent. alcohol to take up moisture; 4, apply liquid albolene to make nipple pliable; 5, the towel is removed and the binder is pinned shut. Such a cleansing is done routinely before each feeding.

Before the mother touches her breasts she cleans her hands with alcohol sponges which are close at hand. About three times a day, 2 per cent. mercurochrome is applied to the areolae and nipples.

About the third day, the breasts have a tendency to become engorged. If the application of hot towels locally does not afford relief and if after the baby's feeding there is still an excess of milk, then a breast pump is used. At the present time, a committee from the Staff of the Philadelphia Lying-In is studying the subject of breast engorgement in an attempt to solve the much-mooted question of the relationship between engorged breasts and fever in puerperium. There has not as yet been time to form conclusions as to the results of the following procedure carried out on half the patients in the hospital. The procedure being experimented upon follows. Fluids are being limited until after milk comes into the breast. Babies are being allowed to feed only five minutes on each breast at each feeding in the attempt to prevent mammary overstimulation during the first few days. As soon as the breasts become engorged on the second, third or fourth days, babies are nursing the breast for the full twenty-minute period—the breast pump is being used if the breasts are not completely emptied. Hot towels are being applied to breasts as soon as engorgement is noticed.

Results in the care of breasts in the immediate past have been good—there has been only one breast abscess in several years which was undeniably the result of lack of breast care. When cracking or maceration or softening of the nipple occurs, the nipple is protected by a rubber nipple shield upon which the baby sucks until the abrasions disappear. Various metallic devices may be sewed to the binder in order to protect the nipples.

Preparation of the mouths of children before each feeding is receiving less attention, for it is thought that mouths figure very little in inflammatory conditions of the breasts.

The routine procedure followed in the attempt to dry the breasts is: Application of a tight, supporting breast binder, use of the time-honored camphorated oil locally two or three times a day, limitation of fluids and administration of magnesium sulphate, 1 ounce, every morning. Breasts are pumped only when they become excessively engorged.

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Incidence and Character of Post-Vaccinal Encephalitis.—Investigation of this malady has been in progress since the expert conference at The Hague in 1926. A great deal of spade work on the study of post-vaccinal encephalitis, as was done by the Rolleston Committee,¹ comments the editor of *The Lancet*,² was necessary to make the story complete, but it is admitted that its labors do not add materially to our knowledge of post-vaccinal nervous disease. The report is read for the adequate picture which it gives of an acute nervous disease with a mortality rate of nearly 50 per cent. continuing intermittently to appear, now here and now there with manifest disregard to the incidence of any known factor other than vaccinia.

Reports from the Netherlands, where the disease is most prevalent, indicate an incidence of one case to every 4,000 first vaccinations with a fatality of 33 per cent. In 1929, vaccination against variola was done on a grand scale—encephalitis appeared in one in every 3,437 children vaccinated between the ages of one and two, and one in 815 vaccinated who were from six to eleven years of age. The fatality was a little less (26.9 per cent.) than that previously mentioned. Encephalitis did not occur in any of the 16,000 infants under twelve months of age. There was no certain relation between the intensity of the local reaction after vaccination and the occurrence of encephalitis, and in no case was there anything like a generalized vaccinia.

In England during 1928 and 1929, ninety cases of post-vaccinal encephalitis were reported from about a million and a half vaccinations, i.e., one case in every 48,000 first vaccinations. Some large and populous communities, where plenty of vaccination was being done, escaped encephalitis: there was a notable grouping of cases in other similar areas. There were four instances of familial incidence, and one case in each family died. Since the youngest patient was one year and eight months and the oldest fifty-five years of age, one cannot say dogmatically that post-vaccinal encephalitis is a dis-

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ease only of children vaccinated between five and fifteen. It occurs at times in revaccinated cases.

In Asia, Africa and Australia, there is no record of encephalitis despite the enormous numbers of adult vaccinations. Fifteen million vaccinations were done in Bengal alone in 1928. It rarely occurs in Canada or in the United States. In Mexico, Central America and South America, no cases have been reported.

In Germany, from 1927 to 1929, there were fifty cases with fifteen deaths or one case for every 750,000 first vaccinations. Most of the cases occurred in children two years of age. The period of incubation appeared to be eleven days. All of the six cases occurring after revaccination died. Sixty-five case reports come from Austria. Spain has no cases to report; neither has Greece. Probably the reason why the malady has not occurred in France, Belgium or Italy is that vaccination, as a rule, is done only on infants. Rarely is vaccination done during the years that the disease is so prevalent—five to fifteen.

The English Committee on Vaccination has prepared a commentary on the histological study of twenty-five typical cases. The characteristic lesion is a perivascular demyelination affecting in particular some of the vessels of the white matter of the brain and cord and attended with certain definite tissue reactions among which the inflammatory ones are often the least obvious. The lesions are usually symmetrical. In one case (Editorial¹) the lesions were limited to one side of the spinal cord. Speaking generally, the claim that the lesions of post-vaccinal encephalitis are similar to, if not identical with, those of the nervous affections observed after certain other acute infections, notably the exanthems, has received further support. Attempts made at the Wistar Institute to obtain some evidence of the presence of a virus transmissible to rabbits and monkeys have not yet met with success.

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Hemorrhagic Disease of the Newborn.—This disease, whose incidence is one in every 1,500 newborn babies, appears within the first few hours or several days after birth. The first indication of

its presence may be bleeding from the umbilical cord, bleeding into the intestinal tract, into the subcutaneous or submucous tissues or into the cerebrospinal canal. The prolonged coagulation and bleeding times indicate the nature of the trouble and call for immediate transfusion either intramuscularly, into the peritoneal cavity or into the longitudinal sinus. The two former methods are most convenient in that they do not require blood typing. There is nothing particularly new in the treatment of the following case but it emphasizes the effectiveness of whole blood therapy and the importance of early recognition of the disease perhaps better than résumés of articles on the subject.

Case of E. Burt¹¹ of Philadelphia Lying-In; Baby A, weighing six pounds, was delivered with apparent ease by breech extraction after the mother had been in labor eight hours. As a routine procedure, fifteen cubic centimeters of mother's blood was injected subcutaneously between the scapulae. Ten hours after delivery the baby became very irritable and then desperately ill: search revealed a hematoma in the tissues of the chest wall and of the thigh. The coagulation and bleeding times were each fifteen minutes. Both cisternal and lumbar taps revealed almost pure blood under increased pressure. Twenty cubic centimeters of blood were given at once into the buttocks. Six hours later, ten cubic centimeters of thromboplastin were injected under the skin and followed in six hours by injection of thirty cubic centimeters of whole blood into the peritoneal cavity. Within twenty-eight hours after delivery the coagulation and bleeding time were again normal, and the baby was well on the way to recovery. Shortly after this, however, the baby developed twitching of the face, right arm and leg. This was relieved by a single cisternal puncture. The fluid, under three millimeters Hg. pressure, was less bloody than the first specimen. No further complications developed.

Wassermanns of mother and child were negative in this case: serological findings are of prognostic importance, for in the presence of congenital lues the treatment outlined above is ineffective (Burt¹¹).

Intracranial Hemorrhage of the Newborn.—This complication, whether the result of a difficult forceps delivery, breech extraction, very rapid spontaneous delivery or immaturity of the blood-vessels is first manifested by irritability and refusal to nurse. These symptoms are rapidly followed by intermittent cyanosis, persistent high or subnormal temperature, localized muscular twitchings, difficulty in swallowing, and, finally, paralysis and death. Treatment consists of administration of mother's blood and early drainage from the

lateral ventricle, the cisterna magna, or spinal canal. The following case of E. Burt¹¹ illustrates the method of treatment and its results.

Baby B, weighing nine pounds, was delivered by forceps after prolonged labor in a primiparous mother. Twenty hours after delivery, following a period of irritability and absolute refusal to nurse, the baby developed twitching of the muscles of the left side of the face, and the right arm and leg. Intermittent cyanosis developed to so severe a degree that it threatened the life of the child.

Twenty cubic centimeters of cerebrospinal fluid under increased pressure were removed from the cisternal region with partial alleviation of symptoms. The clear first portion of the specimen was followed by almost pure blood. Four hours later another fifteen cubic centimeters were removed. Mother's blood was injected intramuscularly to hasten clotting, although the coagulation and bleeding times were normal.

By the next day the temperature had risen to 101° F. The twitching and intermittent cyanosis persisted until the third drainage, when both signs disappeared. On the following day the baby was out of any immediate danger; however, the left side of the face and the right side of the body remained paralyzed. The drainages were continued daily until the cerebrospinal fluid was clear and the cerebrospinal pressure reduced to normal.

By the eleventh day the baby had regained its birth weight and the paralysis had disappeared from the face and right leg. The right arm regained its movement more slowly.

As a general rule, early relief of pressure as soon as intracranial hemorrhage is suspected is imperative, and will usually prevent a resultant spastic paraplegia if continued long enough. As a prophylactic measure following all difficult deliveries, twenty cubic centimeters of whole mother's blood is injected subcutaneously between the scapulae immediately after birth.

Irradiated Ergosterol in Rickets.—The first indication of the exact nature of any vitamin came in 1926 (Windaus and Hess¹²) with the discovery that ergosterol, when irradiated, became vitamin D. Since then, that statement has been modified into a less sweeping one; namely, that the irradiation of ergosterol produces a number of substances, only one of which is an antirachitic substance. This may be vitamin D proper or its equivalent (Holtz and Schreiber¹³). In 1929, a solution of irradiated ergosterol in oil under the name of viosterol was introduced for the treatment of rickets. At that time the strength was standardized at 100D (100 times the vitamin D strength of cod-liver oil). A preparation of cod-liver oil and viosterol with 5D strength was also put into use. A great deal of confusion has been caused by the differences of intensity of the

irradiated solvents in the preparations in the various countries. When it is taken into consideration that the original French preparation was 40D and the German preparation 2500D, it is very evident that estimate of the degree of potency based solely on number of milligrams of viosterol is unreliable.

As a consequence of early ineffective results in the prophylaxis of rickets by viosterol as compared to cod-liver oil in a series of carefully controlled cases, De Sanctis and Craig,¹⁴ Hess *et al.*,¹⁵ came to the conclusion that viosterol dosage was too low and recommended balancing this deficiency by increasing the potency. Accordingly, in October 1930, the Council on Pharmacy and Chemistry and the Wisconsin Alumni Research Foundation, following the suggestions of the profession at large, raised viosterol in oil, 100D to 250D, and cod-liver oil with viosterol, 5D to 10D.

Vigantol, a 2000D preparation (Hess¹⁶), was used by Sobel and Claman¹⁷ in 1929. They found that craniotabes disappeared in two weeks under its influence and that the open anterior fontanelle diminished in size from four to two fingers in six weeks. In addition, there was marked improvement in behavior, weight and color of the child. Hess¹⁶ discourages the use of vigantol because of its high potency.

Notable in the administration of viosterol is the broad margin of safety in its dosage. The amount given for prophylaxis differs widely. Tyson,¹⁸ at the Philadelphia Lying-In, uses viosterol 250D, three drops a day starting at the end of the first month of age and increasing the dose gradually to ten drops a day by the time the child reaches eighteen to twenty-four months. Of interest is the minute dose required to protect young rats against rickets—1/10,000 milligram as a daily dose (Wright¹⁹). In the treatment of rickets, doses up to fifty drops a day may be used. Viosterol should not be given in a bottle of milk for it tends to float: it is better given by teaspoon with dilute orange juice. It may be used in pregnant mothers with perfect safety.

Using 100D strength in comparatively large doses, Hess *et al.*²⁰ failed to produce toxic symptoms. There was, however, in laboratory animals, a hypercalcemia resulting in calcification of the aorta, coronaries, heart, stomach and kidneys together with mild toxic symptoms. Opitz²¹ reports intensive antirachitic therapy in the form

of viosterol, cod-liver oil and ultraviolet light irradiations to twins fifteen months of age who were being treated prophylactically. The roentgenogram revealed hypercalcification of the diaphyses of long bones of the pelvis, scapulae, clavicles and of other bones of the skeleton. He warned against the danger of hypermineralization of the internal organs. It should be borne in mind that cod-liver oil, in doses of three to four drams a day over an extended time, is equally as effective as viosterol in producing hypercalcemia.

The value of ergosterol lies probably in its ability to raise the deficient calcium phosphate by promoting the absorption of calcium and phosphorus from the bowel (Wright.¹⁹). In the absence of vitamin D there is insufficient absorption of calcium and phosphorus by the intestinal tract and consequent loss of these minerals by bowel. Often the inorganic phosphorus of the serum falls from 5 milligrams to 1.5 milligrams because of this loss. Only an excessive retention of these two minerals will cure the disease. In normal individuals it is thought that the ultraviolet rays convert ergosterol in the skin into vitamin D.

Edelstein,²³ in reporting fifteen cures from severe rickets, mentions that some symptoms are more amenable than others to treatment—dystrophy, and muscle atony being implacable to treatment.

Viosterol should not supplant cod-liver oil or ultraviolet light in the treatment of rickets, for cod-liver oil is still beneficial through its vitamin A content, and light for its general tonic effect and its influence in increasing metabolism. Irradiated milk, in both powdered and fluid form, has antirachitic properties: irradiated cereals, on the other hand, are of little value because of their small sterol content and because cereals are seldom used by an infant before the sixth month.

Nirvanol in Treatment of Chorea.—A brief period of clinical application of the hypnotic nirvanol has been sufficient to prove its efficacy in chorea, particularly in its violent and paralytic forms. As pointed out by Ashby,²⁴ who used the drug in twelve cases, the duration of the disease is lessened and its course is checked before rheumatic infection can do cardiac damage.

Hitherto, the efficacy of drug treatment of chorea has been under suspicion mainly because the various drugs, such as sodium salicylate, chloretone, luminal, milk injections, arsphenamin, liquor

arsenicalis, did not shorten the course of this self-limited disease. Whitaker,²⁵ in treating eleven cases with nirvanol, states that within a week after the skin reaction, there is an improvement or even complete recovery from chorea. In no case was there active chorea one month after its administration.

A typical nirvanol rash develops about the eighth day after daily administration of 3.5 to 4 grains. The rash, usually beginning on the backs of the hands and buttocks, and then spreading to the trunk, where it remains four days, is the signal for discontinuing the drug. At times the occurrence of the rash can be foretold by development of urinary incontinence the night before.

Nirvanol, or phenylethyl hydantoin, a white powder belonging to the barbituric acid group, similar to luminal in that it possesses one less CO group, possesses the power of producing an exanthem more often than any known drug. De Rudder²⁶ thinks that its beneficial action, closely allied to serum sickness, is due to the sudden change at the time of reaction from a blood alkalosis to an acidosis. Lesigang,²⁷ on the other hand, is of the opinion that nirvanol sickness is an allergic phenomenon.

Ketogenic-diet Therapy in Epilepsy.—Disturbances of water metabolism, of supracortical fluid accumulations or of mobility of fluids in provoking convulsive seizures may be brought about by any one of a number of factors. Fay²⁸ brings into focus the multiplicity of mechanisms through his compilation of fairly well recognized etiologic factors. They follow below in condensed and somewhat altered form.

1. Cortical lesions: scars, tumors, arachnoiditis.
2. Pacchionian body lesions: hyperplasia, aplasia, fibrosis, mechanical obstruction through birth injuries.
3. Longitudinal sinus injury or thrombosis.
4. Lateral or sigmoid sinus anomalies or inflammatory changes (as in extension from the mastoid).
5. Jugular foramen stenosis, asymmetry, anomalies (frequently found in patients with idiopathic epilepsy).
6. Venous obstruction due to enlarged thymus or thyroid.
7. Foreign bodies in esophagus, metastatic carcinoma of neck, tonsillar abscesses, Stokes-Adams' disease, anomalies of the heart, cardiac disease with congestive failure.

8. Kidney disease, acute and chronic, with eclampsia, uremia or acute toxic infections in childhood.
9. Colon infections or abnormalities (the colon represents the largest area of fluid absorption and concentration of fecal content).
10. Pancreatic function in regard to insulin and carbohydrate metabolism and water storage. Pituitary interrelation with other glands with reference to metabolism.

Despite the newness of the dehydration treatment in epilepsy, several rather concrete facts, which find direct clinical application, have been established. Not that the major problems involving the biochemical aspects have been clarified—these intricacies await further studies on water and mineral metabolism.

McQuarrie²⁹ gave, in turn, to the same individual isocaloric, high fat, high protein, high carbohydrate and border-line diets in order to determine their relative values. Bartlett *et al.*³⁰ did very much the same thing, paying particular attention to water and mineral metabolism. A high carbohydrate diet favors retention of fluid in the body while a high dextrose, a high protein or a high fat-acid-ash diet favors elimination of fluid. Fluid balance is inseparably bound with mineral content of the food and of the blood. The high protein and high carbohydrate diets have a high mineral content with a positive potassium and sodium balance in the blood; on the other hand, the high fat-acid-ash diets are low in minerals and possess correspondingly a negative calcium, sodium and chlorine balance.

The high dextrose diet shows a negative calcium balance: chemical analysis of the blood after dextrose administrations reveals a drop of 25 per cent. in the chlorid content. The conclusion arrived at is that the degree of dehydration depends upon mineral balance—that diets containing least water and least minerals are the most effective. Dehydration cannot categorically be said to be the only consideration in the treatment of epileptic seizures. If this were not so then protein diet should have the best effects because it causes the most marked excretion of fluids (Bartlett *et al.*³⁰). At times this protein-high diet is ineffective despite the fact that in proteins there are certain "ketogenic" amino acids, such as leucin, tyrosin and phenyl-alanin: the ineffectiveness is probably due to high mineral content.

The value of high fat diet lies probably in the production of certain ketone bodies, such as acetone and ethyl aceto-acetate diacetone alcohol, which seem to have a specific effect on the mechanism of controlling a convulsion (McQuarrie²⁹). Cholesterol, which is closely related to permeability of all membranes, is thought also to have an intimate relationship to occurrence of convulsions (Wright¹⁹). McQuarrie²⁹ makes the significant statement that he has observed patients with epilepsy on a controlled ketogenic diet who apparently are able to take unlimited amounts of water and remain free of convulsions. Dehydration, then, in the narrow sense of the term, is not to be considered the sole factor in controlling convulsions. No cure-all diet or regimen has been found. Hamilton³⁰ remarks that if one method of dehydration is ineffective, another should be tried. In one of his cases of petit mal the ketogenic diet was ineffective in that it failed to produce dehydration. After transferal for awhile to a starvation diet with subsequent return to the ketogenic diet, there was no return of convulsions. Helmholz³⁰ cites a case which was so dehydrated that the mucous membranes were dry and the temperature elevated and yet convulsions continued. Change to a ketogenic diet resulted in a complete control of convulsions. From these experiences it is obvious that no simple principle can be laid down for the treatment of all cases.

In the dietetic application of these principles, Bauer,³¹ taking part in a symposium on epilepsy, mentions among other things some practical points as to the types of food most suitable in treating epileptic children. In the first place, hospitalization is a necessity. Barborka,³² in treating 100 cases with ketogenic diet outside an institution, had 44 per cent. failures. Dehydration should be carried out gradually. Start them off with the amount of fluid that they are accustomed to—say forty ounces—then thirty-two and later twenty-four and sixteen, etc., taking a variable length of time to do this. This will prevent their resorting to subterfuges, such as sucking their wash rags, in order to get the desired fluid. Meat and eggs need not be entirely eliminated from the diet. Vegetables are to be given as dry as within reason, potatoes are to be boiled or baked, cooked cereals should be cooked thick, and there should be no strained food. The well-seasoned and salted soup that every mother in the world thinks is indispensable, because of its nutrition, is outlawed.

In fact, an equal quantity of milk has far more nutrition value. Stewed fruits should be used. Sweets are offenders.

With a well-rounded diet established, convulsions may occur. All right, continues Bauer,³¹ then cut down the amount of food but keep the diet varied and rounded. Cut it down from twenty-four to sixteen and then increase it slowly again to twenty. In summer time two or three ounces of fluid can be added to make up for the perspiration.

Diagnostic Test in Epilepsy.—Nine epileptic children and an equal number of non-epileptics were compared in their reactions to administration of water and ampules of pitressin (McQuarrie³⁰). All the epileptics had convulsions within from fifteen to thirty-six hours, whereas none of the non-epileptics had seizures, although their increase in weight owing to water retention was equally as great as that of children with epilepsy. This procedure has been tentatively proposed as a diagnostic test for epilepsy in questionable cases.

Immunization Against Diphtheria.—France, Canada, Austria and the South American countries are using diphtheria toxoid in preference to toxin-antitoxin in the prophylaxis against diphtheria. At the recommendation of the French Academy of Medicine, a half-million children were vaccinated with toxoid prepared by Ramon.³³ Three injections were made; the first, 0.5 cubic centimeter, the second, 1 cubic centimeter, three weeks later, and the third, 1.5 cubic centimeters, still two weeks later. Within two months there was a negative Schick reaction in from 96 to 100 per cent. of cases that showed a positive reaction before vaccination. Use of Ramon's toxoid in Uruguayan schools (Schiaffino³⁴) at a time when the incidence of diphtheria in the school children of Montevideo was reaching serious proportions, brought forth the conclusion that often a fourth dose of toxoid is necessary because of 26 per cent. of positive Schick reactions following the third dose. Nicolle,³⁵ in Tunis, gave toxoid to 907 individuals. He noted fever in 4 per cent. of patients following the second injection. In children under five there was no reaction. Lapierre,³⁶ who first adopted the use of toxoid in Canada, states that he has encountered some severe reactions following the use of toxoid. However, in many thousand complete vaccinations there was no subsequent positive Schick test. It is generally claimed for toxoid that it is more stable than T-A, gives less reactions, retains

its antigenic properties three times as long (eighteen months), and is not as susceptible to temperature change as T-A. It contains no horse, goat or sheep serum and hence cannot sensitize patients to animal serum protein.

Of other methods in obtaining diphtheria prophylaxis, the most outstanding is that of Löwenstein,³⁷ in which an ointment containing dead diphtheria bacilli as well as diphtheria toxin is rubbed into the skin three times at intervals of two weeks. Immunity develops within a month. This method was tried in four children's institutions in Vienna with consequent high Schick negativity. Jakoff³⁸ is enthusiastic about Löwenstein's "percutaneous" salve after using it in an institution during a diphtheria epidemic. He believes that it is the method of choice in thickly populated asylums. The salve is stated not to produce a negative period, and not to sensitize to sera, while its use avoids its occurrence of constitutional reactions.

Protective inoculation against diphtheria becomes obvious only after at least half the children of the community or institution have been so treated (Otto³⁹). There was no drop in the incidence of diphtheria in Kansas City until 83 per cent. of school children had been vaccinated. Active diphtheria immunization by the T-A method, most popular in the United States, has been warned against by Basch,⁴⁰ in that a negative phase can be produced in active immunization, at which time direct exposure to diphtheria may produce the disease, an occurrence obviated by the use of Löwenstein's salve. Otto³⁹ and Von Bering³⁹ feel, however, that this so-called "negative phase" need cause no worry.

Infant Feeding During the First Two Weeks.—The method now in use in the feeding of babies at the Philadelphia Lying-In under Dr. R. M. Tyson's guidance is one in which simplicity is a characteristic feature. In the first twenty-four hours after birth, babies go to breast every eight hours and remain at each breast for three minutes. Then during the second twenty-four hours babies go to breast every six hours and remain at each breast for five minutes. After that, regular four-hourly schedule is maintained unless an effort is made to stimulate the milk glands: in such a case a three-hourly schedule is resorted to. Babies are weighed before and after feedings, to determine how much milk has been obtained, no matter whether the breasts seem empty or the baby satisfied. An average-

sized baby should get at least two ounces at each feeding: if it does not get that amount, the breasts should be pumped and the deficiency supplied. If the breasts fail to yield two ounces, a complementary feeding known as P.C. No. 1 is given: whole milk, six ounces, water, twelve ounces, dextrimaltose No. 3, one tablespoonful. P.C. No. 1 is given to babies during the first week. A somewhat less dilute formula is given during the second week: this is known as P.C. No. 2: whole milk, six ounces, water, six ounces, dextrimaltose No. 3, one tablespoonful.

Caesarian-section babies do not go to breast for twenty-four hours after birth—instead they are fed with P.C. No. 1 every three hours. If, at the end of twenty-four hours, the condition of the mother permits, the baby goes on regular breast routine, *i.e.*, every eight hours, every six hours, every four hours.

Babies of toxic mothers are not taken to breasts until all symptoms of toxemia have cleared up: in the meantime the mother's breasts are pumped and the milk discarded. The babies, depending on their size, are fed with P.C. No. 1 or No. 2 when they are strong enough or when their mother's condition permits use of the breasts. If they are very small and weak, it is best to feed with dropper or gavage.

The routine care at the present time for prematures is to put the baby in cotton jacket and feed whisky, three drops in one dram of water every three hours for twenty-four hours. After this, skimmed lactic acid milk (skimmed milk, twelve ounces, Karo, one tablespoonful, lactic acid, twenty-four drops) is given, beginning with three to five drams and increasing to an ounce or more depending on the capacity of the baby. Breast milk is preferable to skimmed lactic acid milk. Use of dropper conserves the baby's energy.

Incident to infant feeding is Barbour's⁴⁰ report on the use of phenobarbital in those infants who are unable to "keep food on their stomach." He gave $\frac{1}{8}$ to $\frac{1}{4}$ grain at intervals of four hours or more for periods of one to six months to seventy-six infants, who ranged in age between one week and eight months. Vomiting was checked and disappeared in all of the thirty-three cases showing that symptom. Recurrent colic was markedly benefited: the infants were able to digest and assimilate food better while under its influence. The drug, combined with irradiation, relieved nine cases of

pylorospasm and twelve cases of enterospasm. It seemed to be of definite benefit when used before and after the Rammstedt operation in two cases of pyloric stenosis.

Copper and Iron in Anemias of Infancy.—Ever since iron was found to be a constituent of hemoglobin it has been administered in various forms in the treatment of anemia despite the fact that its absorbability and utilization were questionable. It has been found only recently by Hart *et al.*⁴¹ that its use by the body depends upon the catalytic influence of copper, a normal constituent of the body. They found that iron-free alcoholic extracts of dried beef, liver, yellow corn and lettuce and ash derived from these same substances completely prevent or cure an induced anemia in rats. Consequently, it followed in their minds that the ash and the ash extracts contain in addition to iron some inorganic substance (most probably copper) vitally concerned in hemoglobin building. Perhaps the reason why so little iron given therapeutically is absorbed is that there has been insufficient copper to make it available for the body cells. Working with this thought in mind, Mills⁴² treated ten cases of idiopathic hypochromic anemia by giving capsules containing 2 grams of Blaud's mass, 1.5 milligrams of copper sulphate and 0.017 milligram of phenolphthalein three times a day. Ninety per cent. of cases showed a rise from 50 to 85 per cent. in hemoglobin after variable lengths of time. Dwyer⁴³ used in six cases of primary and secondary anemia a daily dose of 4 milligrams of copper sulphate and 25 milligrams of iron citrate with good results. Unfortunately, neither Mills nor Dwyer published reticulocyte reaction in their cases.

There is a difference of opinion concerning the toxicity of copper. The ingestion of perhaps from 5 to 10 milligrams a day is, according to Mallory,⁴⁴ without danger.

In these few scattered experiments little of permanent value has been contributed toward copper-iron therapy. More thoroughly controlled experimentation with indication of reticulocyte reaction is necessary in order to "run down" these promising leads.

Apropos to the subject of iron therapy is that of the determination by Dorlencourt *et al.*⁴⁵ of the average amount of iron present in breast milk. He found that a liter contains from 1.4 to 7.0 milligrams with an average of 3 milligrams and that there are

variations in amount of iron at different times of the day and that its amount varied according to age. Mothers of anemic infants should receive iron therapy, he maintains, for it has been proven that the iron content of breast milk is increased by giving soluble iron salts by mouth.

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Bacillus Calmette-Guérin in Tuberculosis.—Pros and cons were voiced at length at the International Tuberculosis Conference at Oslo, in August, on the subject of value and safety of protective immunization with *Bacillus Calmette-Guérin*. With the wide difference of opinion as to whether pathogenic variants of *Bacillus Calmette-Guérin* may arise from time to time, the entire question is still an unsettled one. Petroff¹ asks whether the whole world shall be tubercularized by a vaccine of Calmette's living microorganisms or whether we shall let well enough alone and continue the preventative methods of the recent past which have been so successful in reducing mortality.

The storm-center of argument embraces not only viability and non-viability of the *Bacillus Calmette-Guérin* but also stability or non-stability of its virulence. Calmette^{1, 1a} cites the names of Park,

Lange, Ascoli, Chagar, and Professor Neufeld of Robert Koch Institute, Berlin, to support his contention that *Bacillus Calmette-Guérin* is non-virulent for guinea pigs, rabbits or cattle, and ends somewhat dramatically, "only Petroff of Trudeau . . . is opposed to the bacteriologists of the world in his success in increasing virulence of *Bacillus Calmette-Guérin* by animal passage. The declaration of Neufeld that his findings may only be explained as an 'experimental error' permits us to say that we cannot possibly rely on Petroff's experiments." To this Petroff answered with the volley that Calmette should certainly have heard of the work of Watson, Löwenstein, Tzekhnovitzer, Nobel, Bochini, Much and Koschun, who, in addition to himself, have dissociated the germs into R and S colonies. Lesions produced by the R colonies showed a tendency to heal. The S colonies invariably produced progressive tuberculosis in guinea pigs and occasionally in rabbits. And Calmette should certainly be acquainted with the work of Begbie and Mackie and Kraus^{1a} which is in harmony with Petroff's opinion that progressive tuberculosis can be produced in guinea pigs with *Bacillus Calmette-Guérin*. Petroff found, furthermore, that the disease could be transferred from animal to animal without depreciation of virulence in the microorganism. Calmette killed his experimental animals too soon after inoculation, Petroff maintains. The prolonged latent stage in an apparently benign infection cannot be taken as a criterion of the final outcome. Petroff¹ goes on to state his own findings that *Bacillus Calmette-Guérin* is not stable and that there is danger of increase of virulence at any time. He believes in evolution and mutation of all microorganisms and is opposed to the use of living organisms. His view is in accord with that of McIntosh² that the living, but attenuated, virus is not essential to the production of prophylactic immunity. McIntosh quotes the experiences of Hoff-kine with plague vaccine and Wright with typhoid vaccine to substantiate his view. Calmette^{1a} argues the other way, that . . . "only living vaccines cause durable immunity whereas viruses killed by heat, such as plague, cholera or typhoid vaccines can immunize for only a brief time . . . killed tubercle bacilli fail to immunize."

Recently (1931) Professor Dreyer^{2a, 2b} noted that a certain human strain of tubercle bacillus which has been subcultured on artificial media for several years, would grow on ordinary veal-peptone

broth, and, further, that if the inoculum, instead of being floated on the surface of the broth, were submerged in its depths, growth occurred in the form of small granules at the bottom of the flask, the supernatant fluid remaining quite clear. The method results in growth which is very slow and never abundant, but occasionally the tubercle bacilli grown in this manner are very much more virulent than when grown on current media. In applying this technic to two strains of *Bacillus* of Calmette-Guérin, in one of these strains (*Bacillus* Calmette-Guérin one) the deep subcultures produced generalized tuberculosis in all of the twenty-eight guinea pigs inoculated intraperitoneally and severe progressive tuberculosis in all of the twelve rabbits inoculated intravenously. Dreyer has now shown that if *Bacillus* Calmette-Guérin is subcultured on other media than the glycerin-bile-potato, to which Calmette has accustomed it for many years, virulent subcultures can be obtained; all this strengthens Petroff's contention that the human body cannot be compared to glycerin-bile-potato as a medium for the growth of *Bacillus* Calmette-Guérin.

It appears that despite these criticisms the use of *Bacillus* Calmette-Guérin is becoming more widespread, now having been administered to a million babies. England and Austria have been somewhat reluctant in using it, for the feeling is prevalent that stability of the *Bacillus* Calmette-Guérin strain should be carefully substantiated before it is used as a vaccine. In France, *Bacillus* Calmette-Guérin has been administered to over 288,000 children. Calmette claims absolute safety in face of the critical analysis of his statistics by Greenwood and Rosenfeld³ who denied their reliability. In Düsseldorf, Schlossman³ reported favorably on its use. Calmette states mortality from tuberculosis in infants dropped from 15.9 to 3.4 per cent., Kereszturi and Park in New York report a mortality dropping from 8.6 to 1.1 per cent., Iakhis in Ukrانيا, from 16 to 2.4 per cent., Cantacuzene in Roumania, from 25 to 2.3 per cent., through the use of *Bacillus* Calmette-Guérin (Aronson⁴). At Lübeck, a still unexplained tragedy occurred (Editorial⁵), which precipitated a storm of discussion. Two hundred forty-six infants were treated along the lines suggested by Calmette. Of these, fifty became severely ill with tuberculosis and fourteen died. Investigation disclosed loose methods of administration: midwives were al-

lowed to give the vaccine without jurisdiction of the hospital or dispensary. The German Ministry of the Interior, in its official statement of September 10th, stated that the Bacillus Calmette-Guérin sent from the Pasteur Institute was not responsible for the tragedy. Littener⁵ in Tennessee is convinced of the harmlessness of Bacillus Calmette-Guérin after using it in eighty-six cases. In eight weeks' time, 90 per cent. of cases developed tuberculin allergy. Aronson,⁴ of Philadelphia, reports that in treating twenty-two babies, 82 per cent. developed allergy.

Kereszturi and Park⁶ in treating 447 cases asked themselves four questions regarding the giving of Bacillus Calmette-Guérin, and then answered them. Is the procedure simple? Yes. Is it harmless? Yes, there was no fever and no other reaction. Does it give immunity? Some. If so, how long does the protection last? Degree and duration of the immunity cannot as yet be determined. Calmette⁶ believes immunity diminishes at the end of the first twelve months and suggests revaccination by oral method at the end of one and three years.

There have been numerous comments upon Calmette's oral method of administration of the vaccine during the first week of life. One of the most important subjects—the ultimate fate of the bacilli—has hardly been touched upon. Kereszturi *et al.*⁷ suggests the intradermal method as the best as does also Littener⁶ who produced cold abscesses with subcutaneous administration. When the bacilli are given by mouth, resorption from the intestinal canal is variable. Since most of the bacilli are recovered in the stools there can be no certainty of dosage. Utmost care should be taken to be sure that the individual to be vaccinated is free of infection with virulent tubercle bacilli. To this end a thorough physical examination should be done and two negative Von Pirquet tests obtained one week apart before the dose of from .01 to .03 milligram of Bacillus Calmette-Guérin vaccine is given. When tuberculosis does invade a person immunized with Bacillus Calmette-Guérin it does so practically always, according to Le Maire,⁸ in one of the benign forms—tracheobronchial adenopathy with pulmonary epituberculosis, larval type of polyadenopathy with or without splenomegaly and disease of the hilus, or, finally, scrofula. Insufficient time has elapsed to state whether the bacilli after penetrating the intestinal mucous mem-

brane, are immediately destroyed by the tissues, or produce in the mesenteric glands non-progressive or perhaps progressive lesions. The necessity of placing the newly inoculated babies in a non-tuberculous environment for at least eight weeks, at which time immunity becomes established, has been stressed by Rohmer *et al.*,⁹ who reports deaths in three infants who were returned to tuberculous parents after oral administration of vaccine.

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Coeliac Disease.—Recent studies of coeliac disease would suggest that the condition is fundamentally a deficiency disease with superimposed consequential factors. Parsons¹ has recently reviewed certain phases of the clinical and metabolic aspects of this disorder. The clinical features are essentially those of severe gastro-intestinal disturbance with steatorrhea. The diagnosis can usually be made by examining the faeces, which were very well described by Gee in 1888 in the following manner: "Signs of the disease are yielded by the faeces, being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in color as if devoid of bile; yeasty, frothy, an appearance probably due to fermentation; stinking, stench often very great; the hue is somewhat more yellow, otherwise more drab." These characteristics are due chiefly to the high fat content of the faeces, ranging from 40 to 80 per cent. of the dried faeces instead of the normal 20 to 25 per cent. Neutral fat constitutes about 25 per cent. of the total and there is usually a considerable degree of fermentation due to carbohydrate indigestion.

Certain changes in the chemistry of the blood are of interest. The serum calcium is consistently low and the serum phosphate usually subnormal. Associated with these manifestations of disturbed mineral metabolism there frequently occur delayed ossification, osteoporosis, and, in some cases, rachitic changes. Fractures occur frequently. Tetany is commonly present when the serum calcium concentration falls below 7 milligrams per 100 cubic centimeters. MacLean and Sullivan² made the observation that the tolerance for dextrose is increased in coeliac disease. This was confirmed by Thaysen and Norgaard³ who found that the low blood-sugar curve

following glucose ingestion is not due to deficient absorption, because similar results are obtained by intravenous administration of dextrose. Furthermore, there is an associated rise in the respiratory quotient, indicating increased glucose utilization. They conclude that the cause of the increased tolerance for glucose resides in some undetermined endocrine dysfunction.

It appears probable that the underlying cause of coeliac disease is vitamin D deficiency, due to inadequate absorption of this important factor in the life of the child. Pronounced subjective and objective improvement follows the administration of viosterol or, preferably, ultraviolet irradiation. There is also some evidence suggestive of lack of vitamin A. Some observers believe that the condition is an infantile manifestation of beri-beri, representing deficiency in vitamin B. Haas⁴ believes this to be the case and observes that typical cases of coeliac disease may terminate in beri-beri. The administration of ripe bananas, which are rich in vitamin B, often results in symptomatic improvement.

Dietetic treatment is of the utmost importance. The essentials are: (1) a high protein diet; (2) a moderate amount of carbohydrates, consisting largely of dextrose; (3) a low fat content; (4) an adequate supply of vitamins, calcium, phosphate, and water.

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Familial Study of Tuberculosis.—Opie¹ in his Mary Scott Newbold lecture, in 1927, stressed the necessity of separate consideration of the childhood and adult types of tuberculosis because they differ in pathology, pathogenesis and course.

In summarizing Opie's still-modern conception we find in the childhood type of tuberculosis (1) infection which tends to progressive generalized tuberculosis when there has been contact with a parent or nurse with the active disease, (2) non-selectivity of pulmonary site, (3) rapid spread to adjacent regional lymph nodes and (4) similarity in site of growth and spread to that produced experi-

mentally in animals. On the other hand, in the adult type there is (1) general insusceptibility to the infection to those, such as doctor and nurse, who are constantly in contact with the disease, (2) apical selectivity of site with tendency to fibrocaseose localization, (3) absence of tendency to spread to regional hilus lymph nodes, and (4) dissimilarity to the tuberculosis produced experimentally in laboratory animals. Laboratory animals contract the adult type of tuberculosis only when they have been previously infected with the tubercle bacillus. There is very little, if any, evidence that the adult type of tuberculosis is the result of childhood infection through the gastro-intestinal tract—contrary to the opinion of Fishberg, Pottenger and Professor Ronzoni. Inactive tuberculosis contracted in childhood produces an immunity which is quite evanescent: the tuberculosis found in adolescence is most usually a reinfection. The latent tuberculosis of childhood is always likely to be transformed into active disease.

In 1925, Opie and McPhedran^{1, 2} began a study, still in progress, of the incidence, pathogenesis and method of spread of pulmonary tuberculosis in 400 families. It was found that in these families exposed to open tuberculosis, the children with latent lesions gradually developed clinically active disease. The wife of an actively tuberculous husband has about a 50 per cent. chance of contracting tuberculosis after approximately eight years of contact. Figures present the facts more convincingly than do generalities in this familial study. In families (1) where one member has active tuberculosis the incidence of manifest and open tuberculosis was high: of the children 80 per cent. showed positive tuberculin reaction and 30 per cent. showed latent infection by roentgenogram, (2) where there is latent tuberculosis without appearance of tubercle bacilli in the sputum, the incidence of latent tuberculosis is fairly high, (3) where there is only suspected tuberculosis the incidence of tuberculosis was not above the general average of the population: of the children under ten, 30 per cent. were sensitive to tuberculin and 10 per cent. showed latent lesions by roentgenogram. There has been no significant lessening of incidence of tuberculous infection in childhood to correspond with the diminution of mortality from tuberculosis during the past few years.

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Tuberculosis in Jamaica.—Sponsored by Sir Reginald Edward Stubbs, Governor of Jamaica, and others, a study of tuberculosis in Jamaica has recently been completed by Opie and Isaacs.¹ In Jamaica, where tuberculosis is one of the chief causes of illness, there is a woeful lack of facilities in combating the disease. Instead of being sent to a hospital, which unfortunately does not exist there, tuberculous patients in the last stages of the disease are assigned to poorhouses in Kingston and St. Andrew. From 1924 to 1927 the average period of stay in these poorhouses was only twenty-six days, terminating in death. It is difficult to reach a true estimate of the ravages of the disease since less than half the death reports are certified by a physician, and then in loose equivocal terms.

This hotbed of tuberculosis offers the opportunity of comparison between tropical and temperate zone pathogenicity. Transmission of the disease from one member of a family to another, occurring slowly and insidiously in the United States, is a rapid and very obvious process in Jamaica where the wife and a tuberculous husband may contract the disease within a few months. Crowding of people in conspicuously unsanitary tenement yards, where promiscuous relations are the rule, accounts for the high incidence and rapid transmission in cities: in the country, on the other hand, incidence is lower. During the course of the disease—usually about nine months as contrasted with twenty-five months in the United States—tuberculi bacilli are expectorated in numbers considerably larger, according to the Gaffky method of counting, than in Philadelphia.

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Tuberculosis in School Children.—A general survey of tuberculosis in 4,000 public and high school children of Philadelphia by Opie *et al.*^{46, 47} was carried out with the thought in mind of determining the prevalence of the disease, of working out the most de-

pendable method of recognition, of attempting to discover the disease before it had undermined health, and of preventing, if possible, further progress of the lesions. As to prevalence—0.5 per cent. of all children showed manifest tuberculosis, 2 per cent. showed the childhood type of lesion, 1 per cent. of adolescents from fifteen to eighteen years of age showed latent apical tuberculosis. Adolescent girls were twice more often infected with manifest tuberculosis than boys. Colored children showed active lesions relatively four times more frequently than white children.

The presence of tuberculosis was determined by Roentgen-ray and by tuberculin tests. Early lesions which were not found by roentgenogram did not escape detection by the tuberculin reaction. Complete reliance may be placed in the tuberculin test when one considers the abundant evidence supporting the view that the intensity of the test lessens and finally disappears with the healing of the tuberculosis lesion (Opie). Tracheobronchial lymph-nodes are not demonstrable by roentgenogram unless they are calcified or very large (Opie).

Granted a prevalence of tuberculosis in 37 per cent. of children five years old to 80 per cent. of those fifteen years of age, what are criteria in evaluating the innocuous from the dangerous cases? Opie⁴⁰ concludes that in apparently healthy children the following characteristics may be considered relatively innocuous: positive tuberculin test with negative roentgenologic examination, calcified circumscribed pulmonary nodules, most cases of roentgenogram positive tracheobronchial lymph-node disease (tracheobronchial lymph-nodes are not demonstrable by roentgenogram unless they are calcified or very large (Opie). The dangerous cases are divided into two categories; those (1.75 per cent.) which should receive special care in open-air schools when they show (1) latent roentgenogram-positive childhood type of tuberculosis with tracheobronchial lymph-node involvement; (2) extensive tracheobronchial lymph-node disease in the presence of an intense tuberculin reaction or exposure to open tuberculosis; (3) latent adult type of tuberculosis; (4) arrested pulmonary tuberculosis, and (5) strong tuberculin reaction in a poorly nourished body. The other category of dangerous cases (0.65 per cent.) whose lesions are so advanced as to necessitate treatment in sanatoria, are those showing (1) tuberculous lesions with positive

symptoms and physical signs; (2) progressive latent roentgenogram-positive pulmonary lesions, and (3) massive uncalcified tracheo-bronchial tuberculosis.

THE DRINKER RESPIRATOR

This device, which has figured not without dramatic appeal in the newspapers during the past few months, was developed at the Harvard School of Public Health by the man whose name it bears. It comes to meet the inadequacies of all previous methods of resuscitation. The Schäfer prone-pressure method, as well as devices for inhalation of oxygen-carbon dioxid mixtures, are totally impractical when it becomes necessary to continue artificial respiration for hours or days. As stated succinctly by Murphy and Coyne,¹ the treatment of asphyxia has a twofold object: it should initiate respiration, but it should also satisfy respiratory needs until normal breathing is established. The usual methods of treating asphyxia are inefficient in the latter respect. Even the lowly experimental animal has been benefited by the machine for not infrequently an over-narcotized animal is kept breathing by the respirator until it regains its respiratory power. Following the original article of Drinker and Shaw in 1929 came Von Wachenfeldt's² report (1930) of saving twenty-six of thirty-two infants in his respirator. His work was independent of that of Drinker.

The mechanics of the adult and infant apparatuses, the latter built largely through the efforts of D. P. Murphy, are quite well known. The principle is sound, the method has been demonstrated to be practical and the machine has now reached a high degree of perfection. As described by Drinker and Shaw,^{3, 4} it is an air-tight chamber in which the body is enclosed with the head projecting through a rubber dam at one end. The chest of the patient rises and falls in response to recurring negative pressures (not alternating negative and positive pressures) created within the chamber by means of an air pump. The temperature of the air is under control. Bedpans may be introduced into the respirator if necessary. The motor may be turned off at any time after the patient begins to breathe of his own accord: then the compartment may be used as a plethysmograph to measure accurately, by means of a spirometer, the voluntary respiratory exchange.

The published reports of 100 or more cases of both adults and infants all show that thus far the machine has had a fine success. Although detailed studies of lung structure at death are yet to be reported upon, the clinical results do not show as yet any lung damage. There is no danger of rupture of the lung (Drinker, *et al.*⁵) as long as the negative pressure remains within its customary 12 to 18 centimeters of water in combating complete respiratory paralysis or within the boundaries of 8 to 10 centimeters in infants. Theoretically, complications may arise, according to Murphy,⁶ when there are mucous plugs in the smaller bronchioles. With each succeeding negative pressure the plug is conceivably pushed farther into the terminal bronchioles until it produces partial pulmonary collapse and atelectasis. Alveoli containing imprisoned air may rupture as the result of added strain of outside negative pressure. None of these possibilities have been substantiated by necropsy.

It is of utmost importance to change the patient's position at intervals in order to prevent pulmonary congestion.

The respiratory failure of acute poliomyelitis is relieved and cyanosis is prevented (Drinker, *et al.*⁵). The following report comes from Doctor Blackfan of the Children's Hospital in Boston:

E. B., a boy of nine in the acute stage of a paralysis which spread to involve both arms and the intercostal muscles. Respirations were rapid and diaphragmatic in character. He was placed periodically for sixteen days in the respirator, spending about half the time in the machine during the first week and one-third of the time in it the second week. When placed in the machine, the boy's sleeplessness was relieved, his anxious attitude was changed to that of a sense of security. Very significant was his frequent request to be returned to the respirator. The respiratory rate maintained was between 25 and 35. About nine months after the onset of the illness, the boy was able voluntarily to expand his chest 2½ inches whereas previously he had had only a ½ inch expansion.

Blackfan believes that the machine will be a great asset in the after-treatment of intercostal muscles and in the avoidance of congestive respiratory infections: treatment with those points in view was undertaken over a period of several months in the case just quoted.

Of seventeen cases of carbon monoxid poisoning brought to Bellevue Hospital in New York and treated in the respirator, nine recovered. Oxygen and carbon-dioxid inhalations were used as preliminary measures. Respiratory paralysis in cases of alcoholic coma, morphine, heroin or barbital poisoning and drowning have been

successfully combated (Drinker, *et al.*⁵). The following recounts a case of postoperative respiratory failure:

A woman of twenty-two was operated upon for scoliosis which had developed as a result of poliomyelitis in childhood. She had been suffering with inadequate upper respiratory muscular control. For three days following the operation she was cyanotic and apprehensive. On the eleventh day she became badly cyanosed and became rapidly unconscious. When placed in the respirator, she regained consciousness and fell into a deep sleep. For ten days she had recourse to the respirator. Each time her pulse would drop from 140 to 120. For about a month she was placed in it at night. Two months after the operation she was taken home despite severe heart disease. She died suddenly three months after her operation.

As a means of treatment of asphyxia neonatorum, the infant respirator is endorsed by those, such as Miss Schlegel, R.N., of the Philadelphia Lying-In, who are constantly using the apparatus. She mentions the following cases:

Baby P. had a difficult high forceps delivery of a transverse arrest. The heart was beating, but there were no respirations. There was facial paralysis and a deep dépression over the left temple as result of forceps application. After fifteen minutes in the respirator, regular breathing was established.

Baby C., seven months, position transverse, delivered by version. It was breathing normally at birth. Nine days after birth apnea and cyanosis suddenly developed for some unknown reason. The baby was rushed to the respirator where it was kept at intervals over a period of twelve days. During that time it had forty-one attacks of apnea lasting on an average of 19.8 minutes each. It was placed in the respirator thirty-five times. Six months have now passed. The baby is gaining in weight and is to all appearances quite healthy.

Baby D., seven months, delivered by breech extraction. The baby gasped once or twice and cried several times. The heart action was good. It was sent to the nursery and given routine premature care. About five hours later the baby suddenly stopped breathing. It was rushed to the respirator and after being in it for two minutes began crying and breathing regularly. For ten minutes the motor was turned off while considerable mucus was aspirated from the throat and nose. Because of the poor quality of the respirations the machine was turned on again for about an hour. The baby was placed in a hot bed for another two hours when it developed another cyanotic attack and stopped breathing. Again it was placed in the respirator: the motor was turned on for one-minute intervals four times during the next half hour. After gasping and breathing for an hour the baby died despite the aid of the respirator.

Murphy and Coyne¹ stress the necessity of preliminary clearing of mucus from the nasopharynx by suction through a soft rubber catheter. In their successful treatment of five severely asphyxiated infants at the Boston Lying-In, they noted the time which elapsed between the inception of artificial respiration and the first inde-

pendent breath taken by the infant. In three of these infants, the first spontaneous inspiratory effort was not observed until more than five minutes had passed; in the fourth case there was no spontaneous respiration until sixty-four minutes had elapsed.

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THE WHITE HOUSE CONFERENCE ON CHILD HEALTH AND PROTECTION

Written by an unsigned master hand. *The New York Times* of November 20, 1930, has this to say editorially about the second annual White House Conference on Child Health at Washington:

A great engineer with a great affection for children is likely to do something for them if the opportunity comes his way. President Hoover, with his well-known liking for boys and girls, was bound to attempt measures for the protection, conservation and improvement of the young lives whose course will coincide with that of this nation in coming years. The wisdom of his heart is fully backed by the intelligence of his mind, and the White House Conference on Child Health and Protection will have the interest and support of every mother and father and every friend of children.

For more than a year a thousand leaders chosen from many fields of child welfare work have been gathering facts in preparation for the present conference. No area of the country has been overlooked. No influence having a bearing on our children's lives, present or future, has been neglected. In his address to the opening session Mr. Hoover said that the child's province is one of joy and good humor. It should be, and to many adults looking back through a rosy haze childhood seems a time of light-hearted freedom, though there is testimony to the contrary from a few accurate memories. But however this may be, as the recommendations of the conference committees are carried out, childhood will in fact become brighter.

The problems confronting the conference are innumerable. Divided for

convenience into four sections, each division has already discovered that apparently simple questions lead in the answering to endless new ones, often overlapping and mingling with investigations in other fields. Consideration of child health runs backward into prenatal studies and forward to family relations. Education cannot ignore health, emotional life nor neighborhood influences. Thirty-five million normal children must be given the opportunity to develop to their full capacity, but interest in them must not rule out devotion to the ten million variously deficient through improper nourishment, physical handicaps or twisted minds. One may say confidently that a sound body is the first essential, only to be met by the primary importance of a secure and hospitable environment. Concrete evidence to the extent of many thousands of cases has been gathered by each committee in proof of the importance of its recommendations. The family and parent education section demonstrates convincingly the necessity of giving every child a home where he is loved, protected and encouraged. Among the workers in rural districts there is an equally emphatic demand for a program which will give country boys and girls a chance level with that of their city cousins.

It is the admirable function of the conference to balance and unite all the efforts of all the members. President Hoover is right in saying that these are matters to stir a nation. They are beneath the dignity of no one. Mistakes may be made, not only in individual lines of direction but in the coördination of the whole work. But those mistakes will not be faults of motive or intention. The delegates to this White House convention are truly representative of the millions of fathers and mothers seeking better health, livelier minds and greater happiness for their children than they have had themselves. In the reports and the personalities of the men and women whom President Hoover has enlisted for this work we have at once a summation of all the evidence available and the consummation of hopes and ideals.

RECENT ADVANCES IN SURGERY *

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ANESTHESIA

Anesthetic Agents.—The introduction of new drugs for the induction of anesthesia is evidence of the continued efforts to improve anesthesia, particularly from the standpoint of postoperative complications. Experience with some of the newer drugs has led to the conclusion that, in many cases, the interests of both patient and surgeon can best be served by combining the use of two or more agents in the production of anesthesia. When sodium *iso*-amylethyl barbiturate (sodium amytal) was originally introduced as an intravenous anesthetic for man, it was thought that it could be used as the sole anesthetic agent, and thus the objectionable features of inhalation anesthesia could be avoided. Experience showed, however, that doses large enough to produce complete anesthesia were sometimes followed by untoward reactions, such as delirium, pulmonary edema, and bronchopneumonia. The recent reports of Lundy, Grandstaff, Zerfas and McCallum, and Mason and Baker indicate that sodium *iso*-amylethyl barbiturate has been, in the main, relegated to the rôle of an adjunct in anesthesia. Lundy¹¹³ pointed out that the drug is essentially an antispasmodic and hypnotic. As a hypnotic it may be used in moderate doses, by mouth or intravenously, in preparing patients for operation. In this manner the dangers of the drug are greatly decreased, and its beneficial effects in adding to the comfort of the patient are retained. As an antispasmodic, sodium *iso*-amylethyl barbiturate is useful in non-surgical cases, and it is suggested that this is the particular field to which the drug is adapted. It has proved of value in con-

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trolling the convulsions of tetanus, strychnine poisoning, eclampsia, the toxic effects of local anesthetics, and has been found useful in the treatment of delirium tremens, morphine addiction, migraine, pernicious vomiting, hiccup, postoperative psychosis, and in controlling severe pain that does not respond to morphine.

Within the last year an isomer of sodium *iso*-amylethyl barbiturate, sodium ethyl (1-methylbutyl) barbiturate (nembutal) has been introduced to the profession. It is essentially antispasmodic and sedative; it can be used either orally or intravenously, and its action is similar to that of sodium *iso*-amylethyl barbiturate. Lundy¹¹⁴ reported on its use in 403 cases. He stated that the sedative action of the drug and the fact that an effect equivalent to that of sodium *iso*-amylethyl barbiturate can be obtained with half the amount, thus shortening the period of recovery, make it more advantageous in preparing patients for operation. He advocated, for the average adult, one and a half grains the night before operation, and three grains by mouth forty-five minutes to one hour before operation. A hypodermic of one-sixth to one-quarter grain of morphine and 1/150 grain of atropine sulphate also is given. This prepares the patient for any type of anesthesia, local, spinal, or general. The intravenous dose should not exceed seven and one-half grains.

Tribromethyl alcohol (avertin) was introduced by Willstater and Guisberg in 1927, and since then has been reported on extensively. Many physicians, particularly in Germany, are enthusiastic about its use. From the recent reports of Guttman, Lendle, Nordmann and Edwards, however, one receives the impression that it is not a satisfactory method of inducing surgical anesthesia as a routine, and, if used, should be employed as a basal anesthetic and supplemented by inhalation anesthesia. It has been used in obstetrics and has been found advantageous when given in rather small doses at the end of the first stage of labor.³⁷ A number of deaths have been reported, but Nordmann points out that they may have been due to factors other than the anesthetic itself. In this country the status of the drug is reflected in the recent report of the Council on Pharmacy and Chemistry of the American Medical Association, which deferred definite action on its recognition until "satisfactory studies of its properties, its advantages and its disadvantages have

been made; until the contra-indications have been satisfactorily established; until a generally accepted technic whereby it can be used as satisfactorily as ether has been established; until the action of amylene hydrate in avertin liquid . . . has been determined, and the amount declared. . . .”⁶

Intratracheal Anesthesia.—The intratracheal administration of gas and oxygen, or ether, as a means of inducing anesthesia, is not new. For obvious reasons, it is the method of choice in operations on the head, mouth and lungs. Hewer, in 1926, reported on its use in 3,500 cases, in 1,100 of which operations on the upper part of the abdomen were performed. He pointed out the advantages of the method in the production of quiet, even respirations, maximal muscular relaxation, and protection from operative shock. The method compared favorably with other methods in the incidence of postoperative pulmonary complications. More recently, through the work of Magill, Griffith and others, the method has become more popular for abdominal work. Our own experience with its use in a limited number of operations in the upper part of the abdomen is in support of Hewer’s observations. The even, quiet breathing and satisfactory muscular relaxation are in marked contrast to the forceful, uneven, and often stertorous respirations so commonly seen in the ordinary inhalation anesthesia. The chief disadvantage of the method is that considerable skill is necessary to pass the tube into the trachea without injuring the structures of the nose, throat and larynx.

NERVOUS SYSTEM

Present Status of Sympathetic Ganglionectomy.—The researches of Hunter and Royle on the influence of ramisection in spastic paralysis led to the application of sympathetic ganglionectomy and ramisection to those cases of peripheral vascular disease in which the symptoms are produced alone, or in part, by vasospasm. Adson and Brown, Royle, and others have reported on the operation in Raynaud’s disease, and the results indicate that the disease, in both upper and lower extremities, can be completely and in all probability permanently controlled.

The prognosis in thrombo-angiitis obliterans, so far as cure is concerned, is somewhat different from that in Raynaud’s disease.

The relief obtained depends on the degree of spasm that is present in the collateral vessels. Obviously, the main factor in the production of the circulatory disturbance, the occlusion of a main artery by a thrombus, cannot be altered by removal of the sympathetic ganglia and rami. Consequently, it is advantageous, in considering operation, to know which patients will be benefited by operation. Brown, in 1926, developed a method by which it is possible, following the intravenous injection of typhoid vaccine, to determine the degree of vasodilatation that would be obtained by operation. White has recently advocated a method which he thinks has certain advantages over the intravenous injection of a foreign protein. For the upper extremity he advocates paravertebral injection with procain hydrochlorid, and for the lower extremity one of three methods: (1) spinal anesthesia, producing paralysis to the level of the sixth thoracic segment; (2) direct injection of the lumbar sympathetic ganglion after the technic of Kappis and Labat for posterior splanchnic anesthesia; or (3) injection of the sciatic nerve. White finds that these methods are followed by an increase in surface temperature comparable to that produced by sympathectomy. Beutner has recently advocated the use of acetocholin hydrobromid, a powerful vasodilator, which, after intramuscular injection in doses of 50 to 100 milligrams, produces a marked increase in surface temperature, comparable to that produced in the extremities by resection of the sympathetic ganglia and rami. Morton and Scott¹²⁸ advocate spinal anesthesia as a method of estimating the therapeutic possibilities of sympathectomy, not only in peripheral vascular diseases, but in congenital dilatation of the colon. The results of sympathectomy in Buerger's disease have been less striking than in Raynaud's disease, but the reports indicate that in the majority of cases satisfactory results have been obtained as regards relief of pain and healing of trophic ulcers. Adson and Brown stated that many patients may be saved amputation of a limb if the operation is carried out in the active stage of the disease.

The recognition of the fact that certain forms of scleroderma are associated with vascular changes simulating those in Raynaud's disease has led to the application of sympathectomy in the treatment of that condition. Leriche, in 1924, performed perihumeral sympathectomy, followed by right superior cervical ganglionectomy and

left inferior cervical ramisection in a case of scleroderma, and found that after three years the result was far above expectation.

Recently, Adson, O'Leary and Brown reported on sixteen cases, in three of which the lumbar operation had been done in addition to the cervicothoracic operation. The best results were obtained in the group in which the vasomotor disturbances preceded the development of the scleroderma. There was gradual regression of the sclerodermal changes, but it is pointed out that the best results can be obtained by operating before fibrosis and atrophy of the skin have taken place. In cases in which the sclerodactylia and vasomotor disturbances appeared simultaneously, and those in which the scleroderma was primary, and the vasomotor changes, if present, appeared late in the course of the disease, the operation was followed by the disappearance of the evidences of vasospasm, increase in the mobility of the joints, and healing of trophic ulcers.

Reports published during the last three years indicate that resection of the sympathetic ganglia and rami is of definite value in the treatment of selected cases of congenital dilatation of the colon.^{91, 120, 177, 178} The operation, as originally carried out by Wade and Royle, consisted of left lumbar sympathetic ramisection in which "the white ramus to the first lumbar ganglion and the medial branches from the first, second, third and fourth lumbar ganglia were severed, and the trunk cut across below the fourth ganglion." Wade recently reported on thirteen cases in which this operation was done. In one case the trunk on the right side was divided also. Following the observations of Learmonth and Markowitz^{101, 102} on the function of the sympathetic nerve supply to the distal portion of the colon, rectum and internal sphincter muscle, Rankin and Learmonth simplified the operation and divided the inferior mesenteric nerves and the presacral nerve. They reported beneficial results in one case of congenital dilatation of the colon and one case of rectal obstipation in which this type of operation was performed. Morton and Scott¹²⁹ advocate the use of spinal anesthesia as a method of determining the degree of benefit that will follow sympathectomy in these cases.

The present status of sympathetic ganglionectomy and ramisection in the treatment of arthritis is reflected in a recent article by Rowntree, Adson and Hench, in which they summarized the results

obtained in the seventeen cases in which operation was performed by Adson and his associates. The results have been satisfactory, particularly as regards relief of pain. Patients who will probably be benefited by the operation are those who are comparatively young with progressive non-destructive polyarthritis, chiefly affecting the hands and feet, those with evidences of neurocirculatory disturbances that can be controlled by paralysis of the sympathetic nerves, and those who have been given intensive systematic treatment by the established procedures for a reasonable period and have failed to obtain relief.

Obliterative Vascular Diseases.—Smithwick and White, in considering the treatment of obliterative vascular diseases of the lower extremity, stated that it is rarely necessary to amputate because of pain. They described a method of injecting the nerves of the lower extremity with a view to eliminating pain in order that conservative measures can be used to aid in the healing of indolent ulcerations.

Spasmodic Torticollis.—Frazier and Dandy considered the operative treatment of spasmodic torticollis, and each presented an intradural operation which has given good results. Frazier has attempted to determine as far as possible the muscles at fault and divide the roots from those muscles. He divides or crushes the posterior roots of the first three cervical nerves on one or both sides, depending on whether or not the posterior group of muscles is involved on one or both sides. The spinal accessory nerve on the affected side is then divided. Dandy has sectioned both the motor and sensory roots of the first, second and third cervical nerves, and, when necessary to expose the first motor root, the spinal accessory nerve. The spinal accessory nerve may be divided in the posterior triangle of the neck at that time or at a subsequent time. He later modified the procedure and sectioned only the motor roots, thus preserving sensation.

HEAD AND NECK

Chronic Subluxation of the Temporomaxillary Joint.—The surgical procedures for chronic subluxation of the temporomaxillary joint are reviewed by Morris, Rosenthal and Stapelmohr. This condition varies from a snapping noise as the head of the mandible

glides through its arc in talking, yawning or mastication, to recurring attacks of locking of the joint associated with severe pain. The etiology of the condition has been ascribed to various factors. From a review of the cases in the literature Stapelmohr was unable to discover any relation between the variations in the depth of the glenoid cavity, the height of the zygomatic tubercle and the size or shape of the condyle. Morris stresses the fact that the mechanical disposition of the external ligaments and the posterior thickening of the capsule prevent posterior displacement of the condyle, and that there is no analogous structure to prevent forward displacement. He accepts Pringle's explanation as the causative mechanism of subluxation, namely, that sudden violent contraction of the internal pterygoid, which is attached to the antero-internal aspect of the maniscus, under certain conditions, such as yawning, may displace the cartilage so that the thick central ridge lies obliquely instead of transversely, resulting in locking of the joint. The periarticular structures become stretched and this favors recurrence of the phenomenon. The surgical approach to the joint is by a vertical, curved, or right-angle incision in a triangular area, which, as pointed out by Henderson and New, is devoid of important structures. This triangle, base upward, is bounded behind by the temporal vessels, and in front by the temporofacial nerves. The surgical procedure necessary to affect cure varies in the individual case. Stapelmohr advocates fixation of the disk in a vertical position in front of the condyle as described by Konjetzny. He reported eight cases, in all of which functional results were good. Morris is of the opinion that when capsular relaxation is the predominant factor, the methods of choice are simple plication of the capsule, or the operation devised by Nieden, in which a strip of temporal fascia is turned down and sutured to the capsule, and in cases in which there are pathologic changes in the meniscus, it may be necessary to fix the meniscus to the periosteum of the mandibular fossa, as advocated by Haeber, or to fix the meniscus in a vertical position in front of the condyle, as advocated by Konjetzny, or to remove it entirely.

Hyperparathyroidism.—For years the association of tumors of the parathyroid glands with deficiency of calcium in the bones has been recognized, but it is only within the last few years that hyperparathyroidism has been established as a definite clinical entity.

Barr and Bulger in the last year have added twenty-nine cases of parathyroid tumor to those reviewed by Hoffheinz, making a total of seventy-four cases, in 60 per cent. of which there were lesions of the bones, characterized by osteoporosis of the type seen in osteitis fibrosa, osteomalacia or rickets. Mandl,¹¹⁷ in 1925, removed a parathyroid tumor from a patient with generalized osteitis fibrosa. As the patient improved it was suggested that the parathyroid condition was primary, and not, as had been believed, a compensatory reaction resulting from a primary osseous lesion. Since that time similar cases have been reported by Barr and Bulger, Wilder, Pemberton and Geddie, Richardson, Aub and Bauer, Boyd, Milgram and Stearns, and Compere, in which the diagnosis of hyperparathyroidism had been made on the association of osseous lesions, hypercalcemia, and in some cases a palpable tumor in the neck. In all cases clinical improvement followed removal of the enlarged parathyroid gland, and in one case there was a definite increase in the density of the bones.¹⁸⁵ Postoperative tetany was observed in some cases, but in most cases it was mild and controlled by calcium lactate or parathormone. Most of the tumors on which operation was performed were adenomas. One was classified as a malignant adenoma¹⁸⁵ and one as simple hyperplasia of the gland.¹⁴⁸ Guy recently reported a case without evidence of hyperparathyroidism, in which a benign adenoma of the parathyroid gland was removed, and which later recurred as a malignant growth. The symptoms of hyperparathyroidism vary considerably, but progressive weakness, pain in the bones, bowing of the weight-bearing extremities, polydipsia and polyuria, and gastro-intestinal disorders are common. The serum calcium is elevated, the serum phosphorus is lowered, and there is a negative calcium balance. The exact relationship of the hypercalcemia to osteitis fibrosa had not been determined, but studies indicate that the parathyroid condition is primary.⁵ However, it has been pointed out that changes in the bones have not been observed in experimental hyperparathyroidism and cases of osteitis fibrosa occur in which there is no evidence of hyperparathyroidism.¹⁶ Experience suggests, however, that in all cases of generalized osteoporosis, the serum calcium and phosphorus should be studied and removal of parathyroid tissue should be considered.

THORAX

Malignant Tumors.—The present tendency to extend the application of radiotherapy beyond the field of inoperable and recurrent malignant growths to the field of primary operable growths is manifest by recent reports on the treatment of carcinoma of the breast. During the last few years, particularly in England, radium has been extensively used in the treatment of primary carcinoma of the breast either alone or in combination with Roentgen-ray or surgical procedures, or both. Keynes began the work in 1924, after demonstrating that recurrent nodules could be made to disappear with applications of radium. His experience in 108 cases of primary carcinoma has convinced him that radium is the treatment of choice in the early cases. He prefers interstitial irradiation with platinum needles containing radium, placed in such a way as adequately to irradiate the primary growth and the lymphatic areas. Needles are placed beneath the breast, beneath the pectoral muscles, in the axilla, on the costocoracoid membrane, above the clavicle and in the upper three or four intercostal spaces. It is felt that long exposures (a maximum of seven days) to small doses of radium are more efficacious than short exposures to large doses. When there is some doubt as to the diagnosis, biopsy is done before treatment is started. Tumors begin to shrink in two to three weeks after treatment is started, and if small may entirely disappear within three months. Large tumors may not disappear within six or nine months, or they may shrink to a small size and remain stationary. If the tumor persists after a second course of treatment, it should be removed. Such tumors usually consist of fibrous tissue, but occasionally nests of carcinoma cells are found. Cheatle stressed the fact that it is essential to expose the whole breast because of the inability of the surgeon to know how far the carcinoma cells have spread, and because of the fact that many carcinomas develop on a Schimmelbusch's disease. He contends that radical removal of an operable growth is always safer than inadequate irradiation. Handley, in an attempt to lessen the incidence of recurrence in the fascia along the sternum following radical operation, advocated in 1927, the insertion of radium needles at the inner end of the first three intercostal spaces and above the first rib. These were inserted at the time of opera-

tion. Warwick recently extended this idea, and advocated radical amputation with the insertion of radium needles in the first five interspaces from the sternum to the axilla, in the axilla, in the supra-clavicular fossa, and in the epigastric notch.

Coincident with the extension of the various forms of radiotherapy to the treatment of primary malignant tumors there is considerable interest in the question as to the value of preoperative and postoperative Roentgen-ray treatment of carcinoma of the breast. It is generally conceded, even by those who do not feel that it is indicated as a routine, that Roentgen-ray treatment is of definite value in controlling the pain and discomfort, and sometimes in prolonging life, in cases of recurrence following operation. Greenough, Kahn, Greenough and Daland, and Harrington have been unable to determine that postoperative radiotherapy is of great value in increasing the percentage of three-year and five-year cures. On the other hand, Bruttin, Bevan,²¹ Trout and Peterson, Westermark, Schreiner, and Schmitz have found it of definite value, both as regards the percentage of three-year and five-year cures, and as regards the incidence of recurrences. Perhaps the factor which influences the end-result more than any other single factor or group of factors is the presence or absence of axillary metastasis. Thus, Pfahler and Parry, in a study of 242 cases, found that in cases without lymphatic involvement, operative procedures followed by irradiation gave 89 per cent. of five-year cures as contrasted with 47 per cent. of five-year cures in cases in which lymphatic involvement was found at the time of operation. From a study of statistics from ten clinics in which surgical procedures and postoperative irradiation were used, and from thirty-two clinics in which surgical procedures alone were used, Pfahler and Widmann found an increase of 50 per cent. in the incidence of three-year and five-year cures as a result of postoperative irradiation. The grade of malignancy has been found to influence, to a certain extent, the sensitivity of tumors to the Roentgen-ray, and in this regard it is interesting that in a study of 234 cases, Smith and Bartlett found better results after postoperative irradiation, regardless of the degree of malignancy or the type of operation. O'Brien reviewed the question, and pleaded for the coöperation of the surgeon, pathologist, and radiologist in an effort to obtain better results in malignant disease. He

stated: "Until our present methods of irradiation have been analyzed in conjunction with a standardized surgical procedure with pathological control, prophylactic irradiation must be considered of the greatest value in the treatment of primary mammary cancer."

Aneurysms.—The treatment of aneurysms of the thoracic aorta and innominate artery has been considered by McCarthy. Distal ligation and wiring have been unsatisfactory. He favors the operation of distal arteriovenous anastomosis, advocated by Babcock. The internal jugular vein is anastomosed to the common carotid artery on the principle that by decreasing the peripheral resistance some of the lateral pressure on the artery from the point of anastomosis back to the ventricle is reduced, and consequently the pressure in an aneurysm in that area is reduced. McCarthy reported ten cases, in eight of which operation was performed. The total mortality was 50 per cent. Two of the patients have been able to return to work. The relief of pain, dyspnea and dysphagia following operation was striking. McCarthy feels that the operation will prove to be the treatment of choice for aneurysms in this situation.

Pulmonary Tuberculosis.—Phrenicotomy was introduced by Stuertz, in 1911, for the treatment of unilateral tuberculosis of the lower lobe. Permanent hemiparalysis of the diaphragm was obtained in only about 5 per cent. of cases, and consequently the operation was not extensively used. Felix, in 1922, demonstrated that in 25 to 30 per cent. of persons accessory fibers joined the main stem of the phrenic nerve below the point divided by Stuertz; therefore, he advocated exeresis of the nerve. This operation has been used rather extensively, and has been found to be an efficient method of collapse for treatment in certain cases of pulmonary tuberculosis.^{17, 35, 40, 58, 63, 126} Experience has shown that beneficial results are obtained by its use in lesions of the upper lobes as well as of the lower. Matson stated that the effect depends not so much on the site as on the type of the lesion; that the proliferative types respond best. The beneficial effects of the operation are due to partial collapse of the lung, which is brought about by cessation of diaphragmatic movements¹⁸² and by the gradual elevation of the diaphragm into the thorax.⁴⁴ The reduction in volume of the lung has been estimated at from a sixth to a third.¹²⁰ Aycock and Habliston stated that the benefit of neurectomy is due not only to the

reduction in volume of the lung, but to immobilization of the tissue of the lung. Contrary to the beliefs of some observers, Lemon, as a result of experimentation, is of the opinion that the operation does not protect the affected lung from aspiration infection. Patients who have had the operation find it easier to raise sputum; the amount of the sputum is reduced, fever disappears rapidly and the general condition improves.¹²⁰ Phrenic neurectomy may be used as an independent procedure, as a supplement to artificial pneumothorax, or as a preliminary to extrapleural thoracoplasty. It has been used most extensively as an adjunct to artificial pneumothorax, and in cases in which adhesions prevented a reasonable degree of collapse following that procedure, neurectomy has produced a satisfactory increase in the degree of collapse.⁶⁰ Wirth and Jaski stated that, except in cases of uncontrollable hemorrhage, neurectomy should be done prior to artificial pneumothorax. As a preliminary to extrapleural thoracoplasty, phrenic exeresis may be of value in that it may lead to recovery and render the more radical operation unnecessary.¹²⁰ It may reduce the number of ribs to be removed, reduce the surgical risk by improving the general condition of the patient, and it may act as a test of the integrity of the opposite lung.¹²⁰

GASTRO-INTESTINAL TRACT

Gastric Secretion.—The problem of gastric secretion has been reviewed recently by Ivy. He stated that the humoral mechanism for gastric secretion has been established but whether the humoral agent is secretagogic or hormonic has not been definitely decided. The evidence suggests that it is hormonic, and that the hormone is closely related to, but not identical with, histamin. Fogelson demonstrated that a neutral preparation of gastric mucin, obtained from the hog, was effective in reducing the free hydrochloric acid in dogs with a Pavlov pouch. He applied this principle to the treatment of peptic ulcer. The patients were put on a bland diet, and were given one ounce (thirty cubic centimeters) of powdered mucin with each meal and a one-gram tablet of mucin every hour. Twelve patients who were treated in this manner were relieved of subjective symptoms within three days and had not had recurrence of trouble in periods ranging from two to five months.

Benign Lesions of the Stomach and Duodenum.—The status of the conservative and the radical surgical treatment of benign lesions of the stomach and duodenum has not changed materially during the last year. Most surgeons are agreed that gastric ulcers should be removed, if possible, although it has been shown that simple gastro-enterostomy will give good results in selected cases.^{11, 66} Partial or subtotal gastrectomy for duodenal ulcer is favored by Rossi and Scaloni, Mandl,¹¹⁸ Neller, Reichel, Schur, and Hortolomei in Europe and by Solé, Lewisohn, Berg, and Strauss in America. For ulcers that cannot be resected, Finsterer prefers exclusion of the pylorus and resection to simple gastro-enterostomy. The majority of American and British and certain of the French and Italian surgeons favor the less radical operations, gastro-enterostomy and pyloroplasty. Sirolli reported good results following gastro-enterostomy. The application of these conservative operations to properly selected cases is favored by Bevan,²² Lahey, Judd and Hazeltine and Balfour. The report of Luff on the subsequent history of gastroenterostomy is ample justification for the conservative stand of the British surgeons. Starlinger, although agreeing with those European surgeons who favor resection, stated that the number of known recurrences following resection is gradually increasing. Neller reported 6.6 per cent. of recurrence following resection. Von Haberer,⁷⁵ on the other hand, stated that a part of the recurrences are in reality ulcers that have been overlooked and that if the pylorus is resected recurrences are uncommon.

In the treatment of perforating gastric and duodenal ulcers, Judin advocated primary resection in all cases in which the condition of the patient permits. He reported a mortality of 22.3 per cent. in a series of resections and a mortality rate of 24.4 per cent. in a series in which the ulcer was sutured and gastro-enterostomy was performed. Bryce, Bager, and Williams and Walsh believe that the best results are obtained by simple suture of the ulcer. In the cases reported by these authors, gastro-enterostomy was necessary later in 32 to 50 per cent. of the cases.

Lesions of the Gall-bladder.—A study of the end-results of any given therapeutic procedure establishes facts which can be used in the treatment of disease. It is interesting, therefore, to review the recent reports of Rowlands, von Haberer,⁷⁴ Michelsohn, Pribram,

Sanders, Deaver,⁴⁶ Judd and Walters, and others on the results of surgical procedures on the gall-bladder and biliary tract. A study of these reports reveals that cholecystectomy is the procedure of choice in the majority of cases of cholecystitis with or without stones, that cholecystectomy gives complete relief of digestive disturbances in from 86 to 94.5 per cent. of cases, and that the greatest number of poor results follows removal of gall-bladders in which the chronic inflammation is not associated with stones. Michelsohn, in a study of 712 cases, could not establish a real relationship between the end-results and the duration of the disease. In his experience cases in which there were stones in the common bile-duct or in which the duct was dilated gave twice as many poor results as those without involvement of the duct. Deaver,⁴⁵ on the other hand, found that 59 per cent. of the patients not entirely relieved by cholecystectomy had had digestive disturbances, with attacks of colic, from two to twenty years. He feels that delay in surgical intervention results in the spread of the infection to other organs, and, consequently, that "improvement in morbidity and mortality is dependent on early diagnosis and surgical treatment." Pribram has arrived at the same conclusion. Cattell and Kiefer, because of the high percentage of unsatisfactory results in cases of cholecystitis without stones, advocate conservative treatment in such cases, directing the treatment toward relief of digestive and intestinal symptoms. Postoperative symptoms in the cases in which results are unsatisfactory are due to residual infection in the biliary tract, hepatitis, cholangitis and pancreatitis, incomplete removal or recurrence of stones, and associated conditions such as peptic ulcer, achlorhydria and irritable colon. The reports of Judd on prolonged drainage of the common bile-duct, and of Walters on strictures of the common and hepatic bile-ducts warrant careful study. Several years ago Judd and Mann showed that cholecystectomy was followed by changes in the extrahepatic bile-ducts. It was thought that this was a compensatory reaction on the part of the ducts to assume some of the functions of the gall-bladder. Sutton has recently shown that following cholecystectomy in the dog and when the human gall-bladder has been wholly or partially destroyed by disease, there are changes in the intrahepatic bile-ducts. The epithelium of the ducts is thrown into folds and villi covered with high columnar epithelium, that are his

tologically identical with the mucous folds of the normal gall-bladder. The significance of these changes is as yet unknown.

Lesions of the Appendix.—Reischauer subscribes to the view advanced by Ricker that the initial cause of appendicitis is disturbance of the circulation of the appendix of nervous origin. This neurocirculatory disturbance results in changes in tissue which favor the pathogenic action of bacteria within the lumen of the organ. The cases reported by Ballenger in which acute appendicitis began on the second day following removal of diseased tonsils, and by Freedman in which appendicitis occurred during an epidemic of infection of the upper respiratory tract lend support to the growing conviction that the two conditions may be related etiologically. Wilkie stated that there are two distinct primary acute pathologic conditions affecting the appendix: acute appendicular obstruction, resulting from impaction of a concretion within the lumen, and acute inflammation of the wall of the appendix, which in many cases is a blood-borne infection. He suggested that the tonsils may be a source of infection. Dorsey recently studied the problem from the experimental side and extended the earlier investigations of Rosenow and Dunlap. She found that streptococci isolated from diseased appendixes removed at operation resembled, morphologically and culturally, streptococci isolated from the nasopharynx of patients with appendicitis and those obtained from tonsils of patients with arthritis. By inoculation of animals the streptococci from patients with appendicitis gave a high degree of localization in the appendix whereas the incidence of localization in the joints was low. The streptococci isolated from cases of arthritis, on the other hand, when injected into animals, gave a high degree of localization in the joints, and a low incidence of localization in the appendix. These studies suggest that appendicitis may be a hematogenous intramural streptococcal infection with the nasopharynx as the source of infection.

Polyposis of the Colon.—From a review of recent articles on polyposis of the colon and rectum it becomes apparent that if the incidence of carcinoma of the bowel is to be reduced, more attention must be paid to apparently benign polyps. The fact that carcinoma of the colon and rectum may arise from preexisting polyps is again emphasized by Lockhart-Mummery, Schmieden, Stewart and others.

FitzGibbon, in a study of the polyps in thirteen cases of polyposis, found twenty-four carcinomas. He found that the polyps could be divided into three groups: (1) those which retain the characteristics of normal intestinal mucosa and are strictly benign; (2) those with structural changes in the epithelium and connective tissue which eventually become malignant, and (3) those with undifferentiated epithelial cells that indicate immediate precancerous growth. He was able to trace the site of origin of twenty-two of the twenty-four carcinomas back through unbroken lines to polyps, and concluded, therefore, that "the histogenesis of carcinoma of the colon is mediated through the precancerous formation of polyps. . . ."

Polyposis of the colon is of two types: the adult, acquired type, which occurs secondary to an inflammatory condition of the bowel and the adolescent, congenital type.⁵² The acquired type occurs most frequently as a complication of chronic ulcerative colitis and, according to Bargen and Comfort, occurs in 10 per cent. of cases. This type constituted 80 per cent. of the cases of polyposis studied by these authors; the symptoms were those of ulcerative colitis, and the diagnosis was made by proctoscopic examination and by barium enema. In a certain number of these cases malignancy develops on one or more of the polyps. Treatment consists of fulguration of the polyps that are accessible through the proctoscope if the patient is unable to stand more radical procedures. Bargen and Rankin recently reported a case of polyposis of this type in which treatment was by colectomy.

The congenital type of polyposis is a disease of youth or early middle life, without, apparently, an associated etiologic agent. The two striking features of polyposis of this type are the familial tendency and the frequency with which carcinoma develops on one or more of the polyps. Dukes, in a recent survey of the subject, gave thirteen family pedigrees noted in the literature, and concluded that the disease is inheritable, is transmitted by both male and female, that both sexes are affected, and that the inheritance can be traced through several generations. Barker stated that genealogic studies indicate that the mode of inheritance is by Mendelian dominance. The occurrence of malignancy in this type of polyposis has been variously estimated at from 35 to 48 per cent. and even higher.^{50, 88} Dukes feels that such figures are unreliable because the rate of

malignancy will vary with the age of the patient at the time the case is reported. He stated: "If members of these families survive the other complications of polyposis and the ordinary risks of life, they develop carcinoma of the rectum or colon usually in the early thirties or forties." The treatment is unsatisfactory. Barker reported great improvement in one case by the use of deep Roentgen-ray treatment. Colectomy is the only form of radical treatment that offers a chance of cure.⁵⁰

Because of the inability at times to demonstrate polypoid lesions of the colon by means of the barium enema, Fischer advocated insufflation of the colon with air following the evacuation of the bulk of the barium. Weber recently modified Fischer's technic. After thorough cleansing of the colon, an opaque enema is given, and the patient is asked to expel the enema as completely as possible. The colon is then insufflated with air, under the fluoroscope. Stereo-*roentgenograms* are taken when the entire colon is filled with air. By this method polypoid lesions are visualized as soft, rounded projections into the lumen of the bowel. This procedure has proved of definite value in the diagnosis of generalized polyposis.

Carcinoma of the Rectum.—The accepted method of treatment for all operable growths of the rectum has been excision by one of several standardized methods. Usually this has meant preliminary colostomy and subsequent posterior resection, local excision with end-to-end anastomosis, or combined abdominoperineal resection in one or two stages. Radium and Roentgen-rays have been used in the inoperable cases and in cases in which recurrence followed radical excision. There has been a tendency in certain clinics, because of unsatisfactory surgical end-results, to extend the use of radium, and use it alone, or in conjunction with surgery, in the operable cases. Although good results are reported by certain physicians,²³ most physicians feel that with present knowledge of radium technic and of the radiosensitivity of carcinoma of the rectum, radical excision is the treatment of choice for all operable growths.^{40, 66, 70} Radium is reserved for cases in which the patient will not accept operation, and for border-line and inoperable cases, alone or combined with surgical procedures.^{24, 66, 144} Binkley and Gordon-Watson considered the methods of applying radium to rectal growths and the special indications for each method.

GENITO-URINARY SYSTEM

Prolapse of Uterus.—Counseller and Stacy reviewed the results of various operations for uterine prolapse. For patients of the child-bearing age, with prolapse of mild degree and with retroversion, the modified Gilliam operation, combined with plastic operations on the vagina, was satisfactory in 88.5 per cent. of the cases, and is considered the most satisfactory of internal shortening operations. The Kocher abdominal fixation operation was used if patients were past the menopause and were poor surgical risks, or hysterectomy had been performed. Satisfactory results were obtained in 94.87 per cent. of the cases in which it was used. The Watkins-Wertheim interposition operation gave satisfactory results in 96.6 per cent. of the cases in which it was used. The operation is indicated for patients past the menopause, with a mild to a moderate degree of prolapse, a large cystocele, and a normal-sized uterus. If patients were past the menopause, and marked prolapse and large cystoceles were present, the Mayo vaginal hysterectomy was done, and satisfactory results were obtained in 97 per cent. of the cases. Phaneuf considered the various operative procedures for prolapse. If women are of the child-bearing age his procedure is repair of the cervix, perineum and anterior vaginal wall, and intra-abdominal shortening of the uterosacral and round ligaments. If patients are past the menopause, a modified Watkins-Wertheim-Schauta operation with amputation of the cervix is performed as a routine. When the uterus is atrophic, or when malignancy is suspected, he prefers vaginal hysterectomy.

Chronic Infection of the Cervix.—Moench, C. H. Mayo and Dixon were among the first to recognize that chronic infection of the cervix may act as a focus of infection in arthritis and in certain diseases of the eye. This has again been emphasized by Young, who also pointed out that "with the possible exception of vaginal prolapse in its varying degrees, the most common gynecologic cause of pain in the lower abdomen and pelvis is chronic infection of the cervix." The pain may be in one or both iliac fossas, flank, hip or sacral region and is prone to exaggeration before and during menstruation. He stated that it is possible to demonstrate the origin of the pain by bimanual examination. When chronically infected,

the cervix is more or less fixed, and any attempt to displace it will cause pain at the site complained of by the patient. Young advocated thorough treatment by dilatation and linear cauterization from the internal to the external os. Statham considered the conservative treatment of cervicitis, but stated that when the condition is chronic the treatment is operative, by cautery, amputation, or hysterectomy.

It has been recognized for many years that chronic irritation may lead to the production of carcinoma, and the fact that carcinoma of the cervix occurs more often if cervixes are lacerated, eroded or infected, suggests that there may be an etiologic relationship between cervicitis and carcinoma. Villard and Montel, and Bailey have attempted to determine by histologic examination the nature of this relationship and to identify the precarcinomatous condition. Villard and Montel stated that chronic cervicitis is a precursor of carcinoma through the medium of benign adenoma of inflammatory origin. From a study of 850 specimens, Bailey¹⁰ stated that there are two types of erosion: the congenital, which is in reality an inflammatory lesion in the cervix of a nulliparous woman, and the ulcerative, which usually occurs in the hypertrophied, lacerated, cicatricial cervix of a multiparous woman, and which is characterized by marked chronicity and failure to heal. He concluded: (1) the only factor common to such erosion and carcinoma of the cervix is an associated inflammatory exudate, which varies in intensity; (2) the epithelial reaction to this exudate depends on the intimate contact between the exudate and the epithelium; and (3) this reaction is the intermediate causal factor in the production of carcinoma of the cervix. In squamous epithelium the change is produced by the constant irritation of newly formed epithelial cells. The initial causal factor, which produces the inflammatory exudate, Bailey stated, is bacterial, although chemical factors may play a minor part.

Intravenous Urography.—The first attempt to visualize the urinary tract after the intravenous injection of a radiopaque substance containing iodine was made by Osborne, Sutherland, Scholl, and Rowntree in 1923. They used a 10 per cent. solution of sodium iodid, but found that certain toxic symptoms followed the injection. Although excellent shadows of the bladder were obtained, the method was only partially successful in outlining the renal pelvis and ureters. Roseno, and later Bergerhoff, injected intravenously

a combination of sodium iodid and urea, and found that it afforded both a contrast medium for roentgenologic diagnosis and a test of renal function. The method gave fair success, but was followed occasionally by severe reaction. Ziegler and Köhler, following the oral administration of equal amounts of sodium iodid and urea, found that with pressure over the lower part of the abdomen, compressing the ureters, a fair degree of success could be obtained.

Great advance in intravenous urography came with the synthesis, by Binz and Roth, of a group of compounds combining iodine with the pyridin group. Swick, in 1929, working with von Lichtenberg and Binz, found that one of this group in which the iodine content was increased and a methyl group substituted, was non-toxic and gave satisfactory results as a contrast medium. This substance, uroselectan (the sodium salt of 2 oxo-5-iodo-pyridin-N-acetate) contains 42 per cent. of iodine in organic combination, is neutral, is soluble in water up to 50 per cent. and normally is excreted in the urine up to 90 to 100 per cent. in eight hours. The drug has been tested experimentally by Vallery-Radot and his co-workers, and by Gardner and Heathcote, and has been found by them to be non-toxic. Numerous observers in Europe, England and America have reported on the clinical use of the drug, and all are agreed that its use is a valuable adjunct in urologic diagnosis, but that it does not eliminate the necessity for retrograde pyelography in certain cases.^{38, 39, 84, 163} Von Lichtenberg and Swick found that it gave satisfactory results as the sole diagnostic aid in 75 per cent. of cases, and in 25 per cent. of cases it was necessary to supplement it by cystoscopy and pyelography.

The indications for the use of uroselectan are, in general, in cases in which cystoscopic and retrograde pyelographic procedures are impossible or difficult, as in cases of urethral stricture, severe cystitis, advanced prostatic hypertrophy, ureteral stricture, or calculi, in cases in which the ureters have been transplanted into the sigmoid, and in cases in which the fact of the presence or absence of a second kidney is in doubt because only one ureter can be found on cystoscopic examination. It is contra-indicated in cases of advanced renal destruction with uremia.

Opinion as to the value of uroselectan as a means of estimating renal function is varied. The time of appearance and the concen-

tration of the shadow in the pelvis may give an estimate of the functional capacity of the kidney, but Braasch and Bumpus, and Chwalla pointed out that the substance is not secreted in the same concentration by all kidneys of apparently equal function. They further pointed out that good roentgenograms are sometimes obtained when renal function is definitely impaired. Von Lichtenberg, in a recent article, stated that it will not reveal mild changes in function. The fact that 95 per cent. of the drug is excreted in the urine within six to eight hours has led to the determination of renal function by determining the amount of excreted iodid, by estimating the amount of the excreted iodopyridin compound, and by determining the specific gravity of the urine, which has been found to increase proportionately with the amount of iodine present. The value of the latter procedure has not been satisfactorily determined.²⁶ Von Lichtenberg stated that normally the drug has been eliminated from the blood-stream at the end of four hours, and consequently determinations of the amount of uroselectan in the blood will serve as a test of renal function.

Braasch and Bumpus, and Kretschmer stated that uroselectan, because of its non-irritating quality and its high content of iodine, is an excellent medium for retrograde pyelography, and probably will replace sodium iodid for that purpose. All are agreed that the interpretation of uograms made with uroselectan should be made by one who has had considerable experience in urography.

Solitary Serous Cysts of the Kidney.—The literature of the last few years contains numerous reports on solitary cysts of the kidney. In the main there have been two theories as to the origin of these cysts: (1) they are congenital, and arise from embryonic rests, persistent cystic tubules, or from failure of union of glomeruli and tubules; or (2) they are acquired, and result from some obstruction in the tubules with active renal secretion continuing distal to the obstruction. Latteri reported a case of his own, and reviewed the treatment and results in 188 cases noted in the literature. He concluded that they are congenital and are formed from fragments of the ureter or renal pelvis which became included in the renal cortex during the process of development. He attempted to prove this experimentally. Hepler, in this country, reviewed 249 cases from the literature and added seven of his own. In eighty-two of the

cases there were definite pathologic changes in the kidney associated with the cyst. These changes were chiefly chronic nephritis, tumors, calculi, and anomalies. Hepler and Hinman, in 1925, published experimental work on the production of hydronephrosis,⁸¹ in which it was found that ligation of a branch of the renal artery, with ligation of the ureter, produced dilatation of the pelvis with sacculation of the infarcted area. They explained their results on the basis of the infarcted area offering the least resistance to the increased intrapelvic pressure. Hepler applied this principle to the pathogenesis of solitary renal cysts. He isolated the kidney of a rabbit, fulgurated the papillae and ligated the posterior branch of the renal artery. At necropsy, after eighteen days, a cyst arising from the infarcted area was noted. He contends that the cysts are acquired and arise when lesions of the kidney produce group tubular obstruction, and anemic degeneration of the parenchyma in the same segment of the kidney.

Suprapubic Prostatectomy.—Harris reported on his operation for reformation of the urethra and complete closure of the bladder following suprapubic prostatectomy. He performed the operation in 110 cases with a mortality of 1.8 per cent. Postoperative hemorrhage occurred in four cases, and in the last eighty-eight cases it was not necessary to open the bladder for any reason. Following a course of preoperative preparation in which the bladder is irrigated with potassium permanganate followed by instillations of silver nitrate, the prostate gland is enucleated bimanually. After inserting into the bladder specially lighted bladder retractors, a series of sutures is placed in the prostatic bed in such a way as to control bleeding, to reform the prostatic urethra and obliterate the prostatic cavity. Drainage of the bladder is provided by means of a urethral catheter, and the bladder and abdominal wounds are closed. A specially constructed modification of Young's boomerang needle holder is used to place the sutures in the prostatic bed. The catheter is removed on the tenth day and normal micturition is established. The method is applicable to two-stage operations when the preliminary cystostomy incision is made at least four centimeters from the top of the symphysis and at least one month is allowed to elapse between operations. Harris stated that the comfort of the patient, the simplicity of the after-care, and the shortening of the con-

valescence are in marked contrast to the ordinary suprapubic operation.

BONES AND JOINTS

Congenital Dislocation of the Hip.—Putti and Jaeger emphasize the early recognition and treatment of congenital dislocation of the hip. Doran, describing the work at the Instituto Ortopedico Rizzoli, brings out the fact that through the extensive educational campaign carried on by Putti through medical societies, colleges, schools, nurses and lay organizations, parents are acquainted with the fact that there is a definite familial and hereditary occurrence of congenital dislocation. Consequently they are on the lookout for any signs that may be suggestive, and bring the children for examination early, and as a result many cases are recognized during the first year. The Roentgen-ray signs at this stage are: (1) the nucleus of the upper femoral epiphysis is absent, or, if present, small on the affected side; (2) the top of the femur is some distance from the floor of the acetabulum, and higher than normal; and (3) the roof of the acetabulum is sloping. Putti stated that in the first few months of life the separation is so slight that abduction of the limb at from 45° to 50° is sufficient to bring the head opposite the acetabulum and maintenance of this position with slight pressure to keep the head in contact with the acetabulum for from eight to twelve months will effect a cure. He has devised a triangular wooden frame adjustable at different angles to maintain the desired position. He described the results in twenty-four cases.

Jaeger uses a hip splint of rustless steel fastened to the thorax and pelvis by circular bands and to the foot by a foot piece and leather anklet. Gradual reduction of the dislocated head is made by an adjustable pad placed directly over the trochanter. Many excellent papers have appeared on the subject of congenital dislocation of the hip, by Fairbank, who makes special reference to the anatomy, and by Gangler, Natzler, Herbst, Tillmanns, Deutschländer, Bülow-Hansen, and Souter.

Sarcoma of the Bones.—Copeland, Geschicker and Bloodgood, in a study of 200 cases of sarcoma of the bone, found that 15 per cent. of the cases belonged to the type which has been called Ewing's tumor. They point out that because of its occurrence in young per-

sons, the frequent association of fever and leukocytosis and the roentgenologic picture in the early stages, the condition is commonly mistaken for osteomyelitis. The facts brought out by their study indicate that Ewing's tumor is a malignant sarcoma of bone, and not an endothelioma or a myeloma, and that it probably is either subperiosteal or intracortical in origin.

Pheemister, in reviewing sixty-one cases of sarcoma of the bone, noted ten tumors in which cartilage cells seemed to predominate, and he stated that these tumors "present sufficiently distinct morphologic, clinical, and roentgenologic characteristics to warrant their designation as separate entities." He points out that these chondrosarcomas present islands of hyalin cartilage, mature and immature in the same tumor, and areas of calcification and ossification. Hence, irregular, blotchy shadows are produced on roentgenograms. Such tumors are usually near the end of the shaft of the bone. They may develop in cartilaginous exostosis, and as a rule grow more rapidly than osteogenic sarcoma. Tumor cells may invade the veins and produce a tumor thrombus. From a study of his cases, Pheemister believes that with adequate treatment the prognosis is better than in osteogenic sarcoma.

Herendeen reviewed the Roentgen-ray treatment of tumors of the bone. In the order of their sensitivity to Roentgen-rays the tumors can be classified as: (1) Ewing's tumor; (2) giant-cell tumor; (3) multiple myeloma; (4) osteogenic sarcoma of the destructive type; and (5) osteogenic sarcoma of the sclerosing type. He considered particularly giant-cell tumors, and stated that the results of Roentgen-ray treatment of such tumors are, on the whole, superior to those obtained by surgical measures.

Volkmann's Ischemic Contracture.—This condition presents a difficult orthopedic problem, particularly from the standpoint of treatment. Lewis and Meyerding stress the fact that contracture may follow on injury when bandages, splints, or casts have not been applied. The essential factor in the etiology of the condition seems to be interference with the arterial and particularly with the venous circulation, with formation of the hematoma and resulting fibrosis which produces scarring and contracture of the tissues. As the condition most commonly follows fractures about the elbow joint, particular attention should be paid to the occurrence of induration in

the antecubital fossa and pain in the forearm. If such symptoms occur, adequate treatment, with extension, warm packs, or even incision and drainage of the hematoma may present serious consequences. Meyerding analyzed 128 cases and considered the treatment of patients with varying degrees of deformity. The best results were obtained in cases of young persons with recent injuries. Patients with deformities of several days' or weeks' duration, whose arteries pulsated well and whose hands were warm, responded to treatment with the Jones extension splint. Less favorable response to this form of treatment was obtained if deformities were of several months' duration, if the hands were cold, and if arterial pulsation was diminished, in spite of the fact that the fingers could be brought out straight. In cases of marked deformity, atrophy, and greatly impaired movement of the fingers and wrist, and in very severe cases, surgical treatment by tenotomy and osteotomy resulted in reduction of deformity, but little benefit was derived as far as function was concerned. Impairment of circulation and involvement of the nerves in certain severe cases necessitated amputation. Bailey,⁹ and Hodgson reported cases in which treatment was by a modification of the operation described by Page. After conservative measures had failed to reduce the contractures, the internal condyle with the muscle attachments intact was detached and transferred to a bed made by reflecting the periosteum on the inner side of the ulna at the juncture of the upper and middle thirds. Good functional results were obtained. The value of patience and the value of physiotherapy in the treatment of such contractures cannot be overestimated.

Fracture of the Patella.—Rostock presented a study of the end-results in 154 cases of fracture of the patella. One of four methods of treatment was used: (1) conservative procedures; (2) peripatellar wiring; (3) wire suture, and (4) peripatellar silk or catgut suture. The results, as far as working capacity was concerned, were about the same for all methods of treatment. Osseous union was obtained in only 43 per cent. of the cases in which conservative treatment was used, as contrasted with 63 to 74 per cent. in cases in which the other three methods were used. However, this did not influence the end-result as complete restoration of function occurred in 40 per cent. of the cases of osseous union, and 38 per cent. of those of

fibrous union. Madlener and Paas found that deformity of the patella following fracture had no noteworthy effect on the function of the knee-joint. They found that 11.2 per cent. of the patients treated conservatively had poor results, whereas all of those treated operatively had good results.

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